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Office of Health and Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
Washington, D.C. 20460

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ABSTRACT

This draft document evaluates the mutagenicity and carcinogenicity of cadmium, supplementing an earlier document (Health Assessment Document for Cadmium, May 1981) which dealt with all health effects. Since the earlier document was prepared, a rat inhalation carcinogenicity study has been reported and several epidemiology and mutagenicity papers have been published.

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SUMMARY AND CONCLUSIONS

SUMMARY

Qualitative Assessment

Chronic exposure of rats to aerosols of cadmium chloride at airborne concentrations of 12.5, 25, and 50 ug/m^3 for 18 months followed by an additional nonexposed 13-month period produced significant increases in lung tumors. An 18-month exposure to 20 ug/m^3 also increased lung tumors among exposed rats. A single 30-minute exposure of rats to cadmium oxide did not significantly increase the occurrence of lung tumors in the year that followed. However, increases in testicular degeneration were observed. The estimated total dose in mg/kg was, however, lower than that producing testicular neoplasia following parenteral administration. Intratracheal instillation of cadmium oxide has produced an increase in mammary tumors and an increase in tumors at multiple sites among male rats. Intrathoracic injections of cadmium powder are highly toxic, but when their toxicity is reduced by co-administration of zinc, mesotheliomas develop. Intramuscular or subcutaneous injection of cadmium as metal powder, or as chloride, sulfate, oxide, or sulfide, produces injection-site sarcomas and/or testicular interstitial cell (Leydig cell) tumors after necrosis and regeneration of testicular tissue. A recent study suggests that the incidence of pancreatic islet cell tumors may be increased by administration of cadmium chloride by this route. In addition, injection of cadmium chloride into the prostate has induced tumors of that tissue.

Cadmium appears to be much less potent as a carcinogen by ingestion than by injection or inhalation, regardless of the site of cancer induction. For example, the total dose of inhaled cadmium in the Takenaka et al. (1983) study, in which rats developed a 71% incidence of lung cancer, was about 7 mg

($0.25\ m^3$/day x $0.005\ mg/m^3$ x 365 days/year x 1.5 years). By contrast, in the Schroeder et al. (1965) drinking water study in rats, which had one of the smallest total doses of all the ingestion studies, a total dose of about 60 mg (5 ppm x 0.5 x 0.35 kg x 730 days) induced no cancer responses. If a 10% upper limit of detection of tumors in the Schroeder et al. (1965) study is assumed, the highest reasonable potency for cadmium via ingestion is about 0.0017 (0.1/60), compared with a potency of about 0.1 (0.7/7) for inhalation. While it is possible that cadmium is not at all carcinogenic by ingestion because of very limited absorption, the negative animal evidence can only set an upper limit on the carcinogenic potency of ingested cadmium, which in the rat appears to be about two orders of magnitude less than for inhalation.

The IARC (1982) concluded that sufficient evidence exists to determine that cadmuim is carcinogenic in animals. The IARC was aware of the negative findings following the dietary administration of cadmium chloride by Loser (1980). The marked carcinogenic response of rats to inhalation exposure to aerosols of cadmium chloride was not available to IARC for consideration, nor were the highly suggestive reports of pancreatic islet tumors following parenteral administration of cadmium chloride (Poirier et al. 1983), and of male mammary tumors following intratracheal instillation of cadmium oxide (Sanders and Mahaffey 1984). Apparently the IARC did not consider the intratracheal induction of mesotheliomas reported by Furst et al. (1973) or the induction of prostate tumors by injections of cadmium chloride into that tissue (Scott and Aughey 1979). As a result of these newer investigations, together with additional information suggesting that long-term pulmonary clearance and translocation from one site to another in the body is not based on chemical solubility, the carcinogenic risks of cadmium and its compounds are now seen to be possibly greater than orginally anticipated.

Gene mutation studies in mammalian cell cultures, rec-assays in bacteria, chromosomal nondisjunction studies in intact mammals, and other indicators of mutagenic damage do indicate that cadmium is mutagenic.

Epidemiologic studies reviewed after the May 1981 OHEA Health Assessment Document for Cadmium have not appreciably changed the earlier findings of insufficient evidence of a risk of prostate cancer from exposure to cadmium.

On the other hand, recent evidence from the same studies seems to provide better evidence of a lung cancer risk from exposure to cadmium. Strong evidence is available from the Thun et al. (1984) study that the significant twofold excess risk of lung cancer seen in cadmium smelter workers is probably not due to the presence of arsenic in the plant or to increased smoking by such workers. Thun et al. analyzed both factors as potential confounders and convincingly dismissed both in their updated and enlarged version of the earlier Lemen et al. (1976) study, which also demonstrated a significantly elevated risk of lung cancer.

Varner (1983) in a very preliminary updated and enlarged version of the earlier Lemen et al. study also found a statistically significant excess of lung cancer. Varner noted a dose-response relationship for both lung cancer and total malignant neoplasms with increasing cumulative exposure. Varner indicated that the significant excess risk of lung cancer was probably due to smoking or to the presence of arsenic in the plant. However, he had not had a chance to analyze their impact since his paper was preliminary. It suffers from several problems which must be resolved.

Sorahan and Waterhouse (1983) also noted an unqualified statistically significant risk of lung cancer in their study population via the Standard Mortality Ratio (SMR) method. In addition, a significantly high test statistic was noted for excess lung cancer utilizing the Kneale and Cox "regression models in life tables (RMLT)" method in the "high to moderately exposed" group but not in the "highest exposure" category, although the test-statistic was elevated. Sorahan suggested that the excess might be due to exposure to welding fumes of oxyacetylene. No significantly high test-statistic was found in his "highest exposure" group, however, possibly because of a lack of sensitivity due to small numbers.

In his earlier paper, Sorahan (1981) found the risk of lung cancer to be non-significantly elevated through Standard Mortality Ratios calculated in a retrospective prospective cohort study of workers who began employment before and after the amalgamation of two factories into a nickel-cadmium battery plant.

Armstrong and Kazantzis (1983) also demonstrated a significant risk of lung cancer in workers designated by them as having worked in "low exposure" jobs for a minimum of 10 years. Little sensitivity remained in the "highly exposed" group with which to detect a risk after a minimum of 10 years' employment, and such a significant risk was not shown. Furthermore, only a suggestion of an excessive risk was evident in the "ever mediumly" exposed group of workers with a minimum of 10 years employment. This study, however, does not deal in sufficient detail with latent factors 15 or 20 years after initial exposure in combination with length of employment. Also, 17 different plant populations are combined to form one cohort for study, thus raising the possibility that very little exposure occurred to most members of the cohort.

Holden (1980) reported a significantly excessive risk of lung cancer in "vicinity" workers, which he maintained could have been due to the presence of other metals such as arsenic. No excess risk was seen in the group with the highest exposure, however, Latent factors were not considered, nor was the movement of workers from jobs with high exposure to jobs with low exposure, possibly because of seniority.

Andersson et al. (1982), in their update of the Kjellstrom et al. (1979) study, noted a slight but nonsignificant lung cancer risk in alkaline battery factory workers; however, this observation was based on only three lung cancer deaths occurring to this cohort, and the study also suffers from a "small numbers" problem. In the earlier study, Kjellstrom et al. (1979) observed a slight but nonsignificant excess of lung cancer based on two cases in the same small group of cadmium-nickel battery factory workers.

Inskip and Beral (1982) noted a slightly increased but nonsignificant risk of lung cancer among female residents of two small English villages who presumably were exposed to cadmium-contaminated soil via the oral route. However, again only a small number of lung cancers were observed.

Negative findings of a lung cancer risk cannot be considered useful because of problems concerning lack of power, no consideration of latent effects, or insufficient evidence of exposure to cadmium in the studies in which a lung cancer risk was evaluated.

Overall, the weight of the human epidemiologic evidence is suggestive of a significant risk of lung cancer from exposure to cadmium. The contribution of the confounders, smoking and/or the presence of arsenic, has been shown by Thun et al. (1984) not to have produced the significant risk of lung cancer that they found in their study. Further evidence provided by the Carcinogen Assessment Group, under the assumption that arsenic is additive to the background rate of lung cancer and smoking is multiplicative, indicates that the upper bound for the expected number of lung cancer cases is still significantly below that of the observed number of cases at the $P < 0.05$ level in the Thun et al. study.

Altogether, the human epidemiologic evidence appears to provide limited evidence of lung cancer risk from exposure to cadmium, based on the International Agency for Research on Cancer (IARC) classification system.

Quantitative Assessment

Since humans are exposed to cadmium dust or fumes, and the rats used for study were exposed to cadmium chloride aerosol, a limitation inherent in the use of rat studies for estimating human risk is the possible difference between humans and rats in terms of lung retention of particulates, or between the biological effectiveness of cadmium chloride aerosol administered to rats and the dust and fumes inhaled by workers. Since the data are not clear on this point, assumptions of equal lung uptake and equal effectiveness have been made herein for the purpose of arriving at a preliminary assessment of the human risks.

Given these assumptions, combined with other assumptions and conventions used in quantitative risk assessment procedures, the Takenaka et al. (1983) data on lung carcinomas in rats during lifetime inhalation exposures to cadmium chloride aerosol were analyzed. The result of the analysis is that the upper-bound cancer risk to humans who continuously breathe 1 ug/m^3 of elemental cadmium for a lifetime is 0.15.

Based on respiratory cancer rates from the Thun et al. (1984) study of cadmium smelter workers, the upper-bound cancer risk from lifetime exposure to 1 ug/m^3 of cadmium in the air has a range of 4.3×10^{-6} to 3.8×10^{-2}, with a most plausible estimate of 2.3×10^{-3}. The most plausible estimate is based on "best guesses" for each of a series of terms, that are multiplied to form the final estimate. Because only fragmentary information is available concerning cadmium exposures of workers, and many potential biases exist at a range of almost four orders of magnitude, the human risk is considered to be reasonable. Further detailed analysis and laboratory studies are needed before the large difference between the estimates based on animal and human data are resolved.

CONCLUSIONS

Applying the IARC approach (Appendix B) for classifying the weight-of-evidence for carcinogenicity in experimental animals, lung carcinomas in rats exposed to cadmium chloride aerosol by inhalation provide sufficient evidence for the carcinogenicity of cadmium and certain cadmium compounds in experimental animals along with injection site and testicular tumors in mice and rats given cadmium metal or cadmium salts. No carcinogenic response has been observed with ingested cadmium, and the potency via the oral route is at least 200 times less than via inhalation in experimental animals.

The available human epidemiologic data provide limited evidence, according to the IARC criteria, that airborne concentrations of cadmium and cadmium compounds are carcinogenic in humans, producing a significant risk of lung cancer by the inhalation route.

The overall evidence for carcinogenicity, applying the IARC criteria, places cadmium and cadmium compounds in the 2A category, meaning that they are probably carcinogenic in humans.

The upper-bound unit risk estimate for continuous inhalation exposure at a cadmium concentration of 1 ug/m^3 ranges from 4.3 x 10^{-6} to 3.8 x 10^{-2} with a most plausible estimate of 2.3 x 10^{-3} based on lung cancer from one smelter worker study, although there is considerable uncertainty in these estimates because of the lack of differential exposure in the workplace. Nevertheless, these estimates are regarded as more realistic than the estimate based on the rat inhalation study, which is about 65 times higher.

INTRODUCTION

This document is a review and assessment of the current information relating to the mutagenicity and carcinogenicity of cadmium. It contains a detailed discussion of information on those subjects which became available since the earlier Health Assessment Document for Cadmium was prepared by the Office of Health and Environmental Assessment (OHEA) in May 1981. It includes all pertinent material from the 1981 document but does not attempt to repeat details of the animal carcinogenicity studies discussed there.

MUTAGENICITY

Cadmium has been investigated for its mutagenic potential in both prokaryotic and eukaryotic systems. In the former category are assays for gene mutation and reparable genetic damage in bacteria. In the latter category are gene mutation studies in yeast, Drosophila, and mammalian cells; and chromosomal aberration studies in human and other mammalian cells exposed to cadmium both *in vitro* and *in vivo*. The following is an analysis of the literature pertaining to the mutagenic effects of cadmium.

GENE MUTATIONS IN PROKARYOTES

Gene mutation studies that have been conducted in prokaryotic systems are summarized in Table 1. A discussion of each study follows.

Salmonella Assay

Heddle and Bruce (1977) tested the mutagenic effects of cadmium chloride in the histidine reverse mutation assay using *Salmonella typhimurium* tester strains TA100, TA98, and TA1537. The test compound (purchased from ICN Pharmaceuticals, Plainview, New York) was dissolved in water and used at concentrations of 0.05, 0.5, 5, 50, and 500 ug/plate with and without the application of a metabolic activation system (S9 mix) derived from phenobarbital-induced rat liver homogenate. According to these authors, cadmium chloride did not induce a significant mutagenic response over the control value. The criterion set for a positive response was 50%, or a 1.5-fold increase in the revertant frequency over the negative control or spontaneous frequency. Revertant counts were given only for strain TA100; the spontaneous frequency of revertants in this strain was 140 colonies per plate. The purity of the cadmium chloride test compound was not given in this report.

TABLE 1. MUTAGENICITY EVALUATION OF CADMIUM: GENE MUTATIONS IN PROKARYOTES

Test system	Strain	Cadmium compound	Dose	S9 Activation system	Results	Comments	Reference
Salmonella typhimurium	TA98 TA100 TA1535 TA1537 TA1538	Cadmium chloride aqueous solution	0.05 0.5 5.0 50.0 500 ug/plate	Phenobarbital-induced rat liver	Reported as negative	1. Data are not presented clearly as revertants/plate for each strain. 2. Purity of compound not discussed.	Heddle and Bruce (1977)
Salmonella typhimurium	TA98 TA1535 TA1537	Cadmium red in DMSO	1 ug/mL	Aroclor 1254-induced mouse liver	Reported as negative	1. Data provided only for the preincubation or suspension assay. No data on the spot test given. 2. Only a single dose was employed; no dose-response data.	Milvy and Kay (1978)
Salmonella typhimurium	TA1535 TA1537	Cadmium chloride (solvent not specified)	10, 20, 20, 45, 90 mM	Uninduced mouse liver	Reported as negative	1. Spontaneous reversion data and experimental reversion data have not been given in terms of numbers. 2. Used uninduced mouse liver S9 activation system. 3. No positive controls.	Polukhina et al. (1977)

(continued on the following page)

TABLE 1. (continued)

Test system	Strain	Cadmium compound	Dose	S9 Activation system	Results	Comments	Reference
Salmonella typhimurium	TA98 TA100 TA1535 TA1537 TA1538	Cadmium diethylthiocarbamate in DMSO	1 5 10 100 ug/plate	Aroclor-induced rat liver	Reported positive for TA1538 and TA98 in the absence of S9 activation. Reported weakly positive both in the presence and absence of S9 activation.	1. Lowest effective dose was 10 ug/plate. 2. Reported positive only for one dose. 3. No dose-response relationship.	Hedenstedt et al. (1979)
Bacillus subtilis rec-assay	H17 Rec$^+$ M45 Rec-	Cadmium chloride aqueous solution	0.05 M/plate	None	Reported as weakly (+) positive		Nishioka (1975)
		Cadmium nitrate aqueous solution			Reported as negative		
Bacillus subtilis rec-assay	H17 Rec$^+$ M45 Rec-	Aqueous solutions of cadmium chloride, nitrite, and sulfite	0.005 M/plate	None	Reported as weakly (+) positive	1. Compounds were pure.	Kanematsu et al. (1980)

In an abstract published by Kalinina and Polukhina (1977), cadmium chloride was reported to be nonmutagenic in the Salmonella assay. However, important variables such as the number of strains used, the dosage employed, and the number of revertants per plate were not reported. Polukhina et al. (1977) also reported negative results with cadmium chloride on Salmonella typhimurium strains TA1535 and TA1537 both in the presence and absence of an S9 activation system derived from uninduced mouse liver homogenate. In this report a suspension assay with cadmium chloride concentrations of 10, 20, 30, 45, and 90 mM was employed. Positive and negative control data were not presented in this paper, so it is not possible to know whether or not the assay system was functioning properly. The toxicity of the test compound was not reported by these investigators.

Milvy and Kay (1978) studied the mutagenic effects of cadmium red (cadmium sulfide and selenium), a dye used in the printing industry, using the Salmonella spot test (Ames et al. 1973) and the preincubation assay (Ames et al. 1975). Salmonella typhimurium strains TA1538, TA98, and TA1535 were employed in these studies. The test compound (10 ug) was dissolved in 0.01 mL dimethyl sulfoxide (DMSO) and added to 0.9 mL of incubation mixture for 30 minutes at 37°C with shaking before plating 0.1 mL onto minimal plates. Experiments were carried out both in the presence and absence of an S9 activation system derived from Aroclor 1254-induced mouse liver homogenate. Cadmium red was reported to be nonmutagenic in both tests. However, data were presented only for the suspension assay. These investigators used only one concentration, and hence, no dose-response relationship was demonstrated. The toxicity of the compound for each strain was not reported. Consequently, this study may be regarded as inconclusive.

Hedenstedt et al. (1979) studied the mutagenic effects of cadmium diethyldithiocarbamate (used in rubber and plastic industries) in Salmonella typhimurium strains TA1535, TA1537, TA1538, TA98, and TA100. The concentrations used were 1, 5, 10, 50, and 100 ug/plate. The compound was dissolved in DMSO. Concentrations of 50 and 100 ug/plate were toxic in many of these strains. The concentration of 10 ug/plate exhibited mutagenic activity in strains TA1538 and TA98 in the absence of a metabolic activation (S9) system obtained from Aroclor 1254-induced rat liver homogenate (Ames et al. 1975). In TA 1538 the revertent frequency increased more than twofold at 10 ug/plate, i.e., 26.3 ± 3.7 revertants/plate compared to a control value of 11.8 ± 2.6 revertants/plate in the absence of metabolic activation. In the presence of metabolic activation, the revertant frequencies in treated organisms and controls were the same. In TA98, the revertant frequency was 58.8 ± 2.3 at 10 ug/plate (almost a twofold increase) compared to the control frequency of 31.5 ± 4.2 revertants/plate in the absence of metabolic activation. No data were given for studies in the presence of metabolic activation. Positive control data were not presented, although the authors indicated that positive controls were employed in the experiment. Since both cadmium diethyldithiocarbamate and zinc diethyldithiocarbamate were found to be mutagenic in this study, it may not be appropriate to infer that cadmium was the mutagenic moiety.

Mandel and Ryser (1981) reported the induction of frameshift mutations in Salmonella typhimurium TA1537 and missense mutations in Salmonella typhimurium TA1535 by cadmium chloride in concert with N-methyl-N'-nitro-N-nitrosoguanidine (MNNG). A concentration of 0.5 mM cadmium chloride facilitated a dose-related increase in the induction of mutation frequency by MNNG that was up to tenfold higher than the control value. This synergism was also noted for the induction of forward mutations to 8-azoguanine (8AG) resistance in the HPRTase locus of these strains. In a recent telephone communication (9/25/83), Dr. Ryser indicated that he had further confirmation of the above work, and forwarded a preprint of his forthcoming publication to the Reproductive Effects Assessment Group of the U.S. Environmental Protection Agency.

These studies indicate that cadmium induces mutations in Salmonella typhimurium in a synergistic manner with other mutagenic chemicals. Similar studies have also been reported in rat embryo cultures (Zasukhina et al. 1977).

Escherichia coli WP2 Assay

Venitt and Levy (1974), in a report on the mutagenicity of chromates in the Escherichia coli WP2 mutation system, mentioned that they also tested cadmium compounds for mutagenicity and found them to be negative. These authors did not mention what types of cadmium compounds they employed, nor did they present data to support their negative conclusions.

Bacillus subtilis Rec-Assay

Nishioka (1975) investigated the mutagenicity of cadmium chloride and cadmium nitrate using the rec-assay of Kada et al. (1972). In the rec-assay, which measures reparable DNA damage, differences in growth sensitivities of Bacillus subtilis strains H17 (recombination-competent wild type rec^+) and M45 (recombination-deficient rec^-) to mutagenic chemicals are measured. When a chemical is more inhibitory to rec^- than to rec^+ cells, it is suspected of being mutagenic. Concentrations of 2.5×10^{-7} cells/0.1 mL were streaked outward from the center of agar plates. Aqueous solutions of cadmium chloride and cadmium nitrate (0.05 M) were applied in 0.05 mL aliquots to disks of filter paper (diameter 10 mm) and placed in the centers of the plates, at the starting point of the streaks of rec^+ and rec^- cells. All of the plates were incubated at 37°C for 24 hours. The degree to which bacterial growth was inhibited was indicated by the relative distance (mm) between the edges of the paper disks and the ends of the bacteria streaks. This inhibition of growth is known as "rec- effect" and is expressed as: no difference between rec$^+$ and rec$^-$ plates (-), less than 5 mm difference (+), 5-10 mm difference (++), or more than 10 mm difference (+++). Cadmium nitrate showed no difference in growth inhibition (-), whereas cadmium chloride exhibited a weak positive response (+). Each experiment was repeated three times. These experiments did not use a metabolic activation system. The cadmium compounds used were of reagent grade.

Similar results were obtained by Kanematsu et al. (1980) using the rec-assay. Cadmium chloride, cadmium nitrite, and cadmium sulfate were employed at a concentration of 0.005 M in 0.05 mL aqueous solution. All of these compounds exhibited a weak mutagenic response (+) (growth inhibition zones of 4-5 mm). According to these authors, the test compounds used were of the highest purity commercially available.

GENE MUTATIONS IN YEAST

Cadmium chloride has been investigated for the induction of gene mutations in the yeast Saccharomyces cerevisiae (Table 2) (Takahashi 1972; Putrament et al. 1977). Takahashi (1972) studied the induction of petite mutations (p-mutations) and auxotrophs in the Saccharomyces cerevisiae heterozygous diploid strain C3116. He treated 10^4 cells with 10 (5.5×10^{-5}M), 12 (6.6×10^{-5}M), and 20 ppm (1.1×10^{-4}M) for 2 days (48 hours) at 25°C. After 2 days of growth, the cell number was determined and the cell suspension was diluted to give a concentration of 2.8×10^{-3} cells per mL. One-tenth of the diluted suspension was spread on the YEPD-agar plate and incubated at 28°C. When small colonies appeared on the plate, they were replica-plated onto YEP-glycerol-agar medium and minimal medium. After overnight incubation at 28°C, induced p-mutants and auxotrophs were scored. At the dose of 12 ppm (1.1×10^{-4}M), no p-mutants or auxotrophs were found in the 786 colonies counted; at the dose of 10 ppm, 10

TABLE 2. MUTAGENICITY EVALUATION OF CADMIUM: GENE MUTATIONS IN YEAST AND MAMMALIAN CELL CULTURES

Test system	Strain	Cadmium compound	Dose	S9 Activation system	Results	Comments	Reference
Saccharomyces cerevisiae (Yeast) P-mutants and auxotrophs	C3116	Cadmium chloride	10 12 20 ppm	None	Reported as positive	1. P-mutants may not represent true gene mutations because they arise by damage in mitochondrial DNA. 2. Vague protocol.	Takahashi (1972)
Saccharomyces cerevisiae P-mutants	197/2d	Cadmium chloride	8 ppm	None	Reported as negative	1. Only one concentration of test compound was used. 2. This concentration was too toxic for the cells. 3. No mutants observed in the few survivors.	Putrament et al. (1977)
Mouse lymphoma	L5178Y $TK^{+/-}$	Cadmium chloride	0.05 0.06 0.08 0.11 0.15 ug/mL	None	Reported as weakly positive	1. Application of t-test to determine the significance has been challenged by Clive et al. (1981).	Amacher and Paillet (1980)
Chinese hamster cells	Lung (Don) cells; resistance to 8-azoguanine	Cadmium acetate Cadmium chloride	2.5 5 10 ug/mL	None	Reported as positive	1. Very low survival due to high toxicity. 2. Observations not repeated or confirmed.	Casto (1976)
Chinese hamster cells	Ovary cells (CHO)	Cadmium chloride	2.5 5 5 10 ug/mL	None	Reported as weakly positive	1. Data not presented.	Hsie et al. (1978)
Chinese hamster cells	V79	Cadmium chloride	1×10^{-6}M 2×10^{-6}M 3×10^{-6}M	None	Reported as positive		Ochi and Ohsawa (1983)
Mouse lymphoma	L5178Y $TK^{+/-}$	Cadmium sulfate	0.10 0.15 0.20 0.30 ug/mL	None	Reported as positive		Oberly et al. (1982)

p-mutants and three auxotrophs were detected in the 871 colonies counted; and at the dose of 20 ppm, there were 12 p-mutants and 9 auxotrophs in 1,182 colonies, indicating that cadmium chloride may be mutagenic. In the controls there were five p-mutants and two auxotrophs in 2,875 colonies counted. According to this paper, however, mutants were induced at dosages of 10 ppm and 20 ppm but not at the dosage of 12 ppm. Such erratic fluctuations in mutation frequency, and the low number of mutants, suggest that the positive results may similarly be questionable. Since p-mutants occur by damage involving mitochondrial DNA rather than nuclear DNA, caution should be exercised in assessing the mutagenic potential of chemicals with this system.

Putrament et al. (1977) also reported a negative result in a test for induction of p-mutation by cadmium chloride in Saccharomyces cerevisiae. The concentration of cadmium chloride tested (8 mM) was very toxic, however, and less than 1% of the cells survived a 6-hour incubation in YEP-glucose medium. No increase of p-mutants was observed, and no data were presented. This study is regarded as inconclusive.

GENE MUTATIONS IN MAMMALIAN CELL CULTURES

Gene mutation studies in cultured mammalian cells have also been summarized in Table 2. A discussion of each study follows.

Mouse Lymphoma Assay

Amacher and Paillet (1980) reported that cadmium choloride (ICN Pharmaceuticals) was mutagenic in the mouse lymphoma L5178Y TK$^{+/-}$ assay. When cadmium chloride, dissolved in normal saline, was tested at concentrations of 2.35 x 10^{-7}M (cell survival 100 ± 11%), 3.57 x 10^{-7}M (cell survival 78 ± 24%), 4.5 x 10^{-7}M (cell survival 62 ± 4%), 6.00 x 10^{-7}M (cell survival 38 ± 11%), and 8.00 x 10^{-7}M (cell survival 12 ± 1%), there was a dose-related increase in mutation frequency. The mutation frequencies per 10^4 survivors for the above doses were 0.48 ± 0.01, 0.58 ± 0.06, 0.56 ± 0.05, 0.63 ± 0.16, and 0.68 ± 0.04, respectively. The mutation frequency at the highest nontoxic dosage of 6.00×10^{-7}M was approximately 1.5-fold higher than the control frequency of 0.40 ± 0.03 (survival 100% ± 5). The dose-response curve obtained by Amacher and Paillet (1980) has been criticized by Clive et al. (1981), who claim that the application of a t-test for low numbers of samples to determine significance is misleading.

In a recent study, Oberly et al. (1982) have clearly demonstrated the mutagenicity of cadmium sulfate in mouse lymphoma L5178Y gene mutation assay. The test compound at concentrations of 0.10, 0.15, 0.20, and 0.35 ug/mL resulted in mutation frequency increases of 1.7-fold (survival 81%), 4.0-fold (survival 55%), 10.5-fold (survival 12%), and 9.9-fold (survival 4%), respectively, over the solvent control value.

Chinese Hamster Cell Assay

Casto (1976), in a report submitted to Dr. Richard Troast of the Office of Pesticide Programs, U.S. Environmental Protection Agency, stated that cadmium acetate and cadmium chloride are mutagenic in Chinese hamster-lung cells (Don) as determined by induction of mutations that confer resistance to 8-azoguanine. Cells were treated with 2.5 (1.36×10^{-8}M), 5 (2.72×10^{-8}M), and 10 ug/mL (5.45×10^{-8}M) of cadmium acetate and cadmium chloride, respectively, for 18 hours, followed by 48 hours of expression time. Cadmium acetate induced mutation frequencies of 2.8, 50, and 10 per 10^{-6} survivors, respectively, for the above dosages. The survival rate was 0.70%, 0.92%, and 0.43%, respectively. Cadmium chloride induced mutation frequencies of 6, 7, 14, and 37 per 10^{-6} survivors. The negative control rate was 2 per 10^6 survivors. According to this investigation, both cadmium acetate and cadmium chloride are weakly mutagenic. These results are questionable, however, because of the low survival rates at the high concentrations used. Hsie et al. (1978) also reported cadmium chloride to be weakly mutagenic at the HGPRT locus in the Chinese hamster ovary cells, but no data were presented.

Ochi and Ohsawa (1983) investigated the inducibility of 6-thioguanine-resistant (6TG) mutants in the Chinese hamster cell line, V79, by cadmium chloride. They also investigated single-strand scission of DNA by cadmium chloride in these cells. The frequency of 6TG-resistant mutants was found to increase with increased concentration of cadmium chloride. Single-strand scission of DNA by cadmium was detected in combination with proteinase K digestion of the cell lysates, indicating formation of DNA-protein cross-linking by the metal.

Based on the weight of evidence from the data available from both biological and biochemical procedures, and also on the basis of personal discussion with the authors of the above publications, cadmium is regarded as mutagenic in mammalian cell culture gene mutation assays.

STUDIES IN DROSOPHILA AND OTHER INSECTS

Studies on the genetic effects of cadmium in *Drosophila* are summarized in Table 3. A discussion of each study follows.

Sorsa and Pfeifer (1973) reported that cadmium chloride at concentrations of 1.25 (6.81×10^{-6}M), 2.5 (1.36×10^{-5}M), 5.0 (2.72×10^{-5}M), 10.0 (5.45×10^{-5}M), 20.0 (1.09×10^{-4}M), and 50 mg/L (2.27×10^{-4}M) of media caused significant delay in the development of larvae as compared with controls. In the sex-linked recessive lethal mutation test (Muller-5 test), only one concentration of 50 mg/L (2.72×10^{-4}M) was used, with no indication of mutagenic response. The number of chromosomes tested and the criteria set for scoring the lethals

TABLE 3. MUTAGENICITY EVALUATION OF CADMIUM: GENE MUTATIONS AND CHROMOSOMAL ABERRATIONS IN DROSOPHILA AND OTHER INSECTS

Test system	Cadmium compound	Dosage	Treatment period	Results	Comments	Reference
Drosophila melanogaster sex-linked recessive lethal test	Cadmium chloride	50.0 mg/L (2.72×10^{-4}M)	Larvae feeding	Reported as negative	1. Data not presented. 2. Only one dose was used.	Sorsa and Pfeifer (1973)
Drosophila melanogaster larval development sex chromosome loss sex-linked recessive lethal test	Cadmium chloride	65 mg/L 62 mg/L + 3,000 R X-rays	Larvae feeding	Reported as negative	1. Treatment was done in larvae only.	Ramel and Friberg (1974)
Drosophila melanogaster dominant lethal mutations	Cadmium chloride	5 10 20 ppm	Larvae feeding	Reported as positive	1. Dose-response reported. 2. Confirmation of these results in an independent laboratory would be of interest for comparative purposes.	Vasudev and Krishnamurthy (1979)
Drosophila melanogaster sex-linked recessive lethal test	Cadmium stearate	10-20 mg/L 50-100 mg/L 100 mg/L 3 mg/m^3	5-10 days (feeding larvae) 10-12 days (feeding adults) (feeding larvae) (inhalation adult)	Reported as negative	1. Rationale for selecting the dosage not given.	Sabalina (1968)

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TABLE 3. (continued)

Test system	Cadmium compound	Dosage	Treatment period	Results	Comments	Reference
Drosophila melanogaster sex chromosome loss	Cadmium chloride	62 ppm		Reported as negative	1. No data have been been presented.	Ramel and Magnusson (1979)
Drosophila melanogaster sex-linked recessive lethal test	Cadmium chloride aqueous solution	50 ppm	Larvae feeding	Reported as negative	1. Toxicity was determined. 2. Development and survival was affected by cadmium.	Inoue and Watanabe (1978)
Poekilocerus pictus (grasshopper) testis (meiotic chromosomal)	Cadmium chloride aqueous solution	0.001% 0.01% 0.05% per animal		Reported as positive	1. The effect may be cytotoxic rather than genetic. 2. No controls.	Kumaraswamy and Rajasekarasetty (1977)

were not reported, however, and no data were presented to indicate the sensitivity of different stages of spermatogenesis.

Ramel and Friberg (1974), using a dose of 62 mg (3.32×10^{-4}M) of cadmium chloride/L of media, which was the maximum non-lethal dose in the toxicity test, found a delay in larval development. They also studied the induction of sex chromosome loss. In the sex chromosome loss test, a total of 23,360 chromosomes from the treated group and 28,143 chromosomes from the control group were tested. The frequencies of sex chromosome losses were 0.3% and 0.2% for the treated and the control groups, respectively.

The mutagenic activity of cadmium stearate was studied by Yu. A. Revazova (quoted in Sabalina 1968) in Drosophila melanogaster using the sex-linked recessive lethal test. Flies were fed a medium containing 10-20 mg (5.45×10^{-5}M to 1.09×10^{-4}M) and 50-100 mg (2.72×10^{-4} to 5.45×10^{-4}M) of cadmium stearate/L substrate for 5-10 and 10-12 days, respectively. The number of sex-linked recessive lethal mutations in 805 chromosomes analyzed was 1 (0.12%) for the 5-10 day treatment, and the number of sex-linked recessive lethal mutations in 2,192 chromosomes examined was 8 (0.36%) for the 10-12 day treatment. When larvae were treated with cadmium stearate concentration of 100 mg/L substrate for 12 days and scored for sex-linked recessive lethal mutants in 380 chromosomes, no mutants were discovered. Cadmium stearate was also administered by inhalation to adult flies for 32 hours (4 hours daily for 8 days). The mean cadmium concentration was 3 mg/m^3. The percentage of sex-linked recessive lethal mutations among the 498 chromosomes was reported to be 0.2%. The control frequency of sex-linked recessive lethal mutations was not provided in the paper. The number of chromosomes tested was not adequate in this study. This study provides no evidence of mutagenicity of cadmium in Drosophila, but the scale of the study was too small to be considered an adequate test even if appropriate controls were presented.

Induction of dominant lethal mutations in Drosophila melanogaster with cadmium chloride has been reported by Vasudev and Krishnamurthy (1979). The doses used were 5 (2.72×10^{-5}M), 10 (5.5×10^{-5}M), and 20 ppm (1.1×10^{-4}M). The frequencies of dominant lethals were 11.8%, 14.3%, and 14.3%, respectively, in 1,244, 1,375, and 1,390 eggs counted. The control frequency was 4.83% in 1,076 eggs counted. These investigators performed the experiment according to the procedure described by Shankaranarayanan (1967) and determined the statistical significance to be at the 5% level, although they did not mention the type of statistical test employed. Based on these observations, this study is evaluated as an indicator of a positive response. A comparable study in an independent laboratory would be of interest for comparative purposes.

Inoue and Watanabe (1978) studied the effects of cadmium chloride in the sex-linked recessive lethal test (attached-X method) in Drosophila melanogaster, Oregon-R flies. In this test, the induction of mutations was measured by the reduction in the proportion of males. The sex ratio (0.528) in the experimental group treated with 50 ppm (2.72×10^{-4}M) was not statistically different from the sex ratio of controls (0.54), indicating that cadmium chloride is nonmutagenic. The dosage selected was a maximally tolerated dose. Both positive (AF-2) and negative controls were used in the experiment.

Ramel and Magnusson (1979) failed to detect nondisjunction and sex chromosome loss in Drosophila following treatment of larvae with 62 ppm (3.32×10^{-4}M) of cadmium chloride. No data were presented; therefore, this study cannot be evaluated.

Chromosomal aberrations were observed in the testes of the grasshopper, Poekilocerus pictus, injected abdominally with 0.001 (5.45×10^{-9}M), 0.01

($5.45 \times 10^{-7}M$), and 0.05% ($2.27 \times 10^{-7}M$) cadmium chloride in 0.05 mL volumes (Kumaraswamy and Rajasekarasetty 1977). Stickiness of chromosomes, bridge formation at anaphase-I, and tetraploidy at metaphase were noted. The test cannot be considered adequate, however, because no controls were used and no tabulated data were presented. The possibility of technical artifacts must also be considered, particularly because chromosomal preparations were made by a squash technique, and no controls were used.

CHROMOSOMAL ABERRATIONS IN HUMAN AND OTHER MAMMALIAN SYSTEMS

Chromosomal damage studies of cadmium, both in vitro and in vivo, are summarized in Tables 4 and 5. A discussion of each study follows.

Studies on Human Chromosomes In Vitro

Shiraishi et al. (1972) tested cadmium sulfide for the induction of chromosomal aberrations in cultured human blood lymphocytes. Lymphocytes from a normal human female were cultured for 72 hours at 37°C. At 8 and 4 hours prior to harvesting, the cultures were treated with cadmium sulfide at a concentration of $6.2 \times 10^{-2}M$. Control cultures were incubated similarly, without the addition of cadmium sulfide. Three hours prior to harvesting, cells were treated with 0.02 ug/mL of colcemid to obtain cells in the metaphase stage of mitosis. Chromosome preparations were made with the standard procedure (air-drying technique) and stained with Giemsa stain. Fifty metaphase cells were scored from each treatment group for chromosomal aberrations. The types of aberrations described include chromatid and isochromatid breaks, and symmetrical and asymmetrical translocations. Increased incidences of chromosomal aberrations, 52% in the 4-hour treatment group and 60% in the 8-hour treatment group, were noted over the control value of 0%. This study utilized a blood sample from only one donor; the history of the donor was not discussed. Since only one

TABLE 4. MUTAGENICITY EVALUATION OF CADMIUM: IN VITRO CHROMOSOMAL ABERRATIONS

Test system	Duration of cultures	Cadmium compound	Dosage	Duration of treatment	Activation system	Results	Comments	Reference
Human blood lymphocytes	72 hrs	Cadmium sulfide (solvent not specified)	6.2×10^{-2} ug/mL	4 hrs 8 hrs	None	Reported as positive	1. Blood lymphocytes were derived from only one individual. 2. Only 50 metaphases for each end point were scored. 3. Only one concentration of the test compound was used.	Shiraishi et al. (1972)
Human blood lymphocytes	48 hrs 72 hrs	Cadmium chloride aqueous solution	5×10^{-5}M 5×10^{-6}M	24 hrs 48 hrs 72 hrs	None	Reported as negative	1. Toxicity was determined. 2. Appropriate dosages used. 3. 100 metaphases scored for each point.	Dekundt and Deminatti (1978)
Human blood lymphocytes	48 hrs	Cadmium chloride aqueous solution		48 hrs	None	Reported as negative	1. Data were not provided. 2. Concentrations of the test compound not specified.	Paton and Allison (1972)
Cell line WI38 and MCR5	24 hrs			24 hrs		Reported as negative		
Human blood lymphocytes G_0 stage	48 hrs	Cadmium acetate aqueous solution	10^{-8} 10^{-7} 10^{-6} 10^{-5} 10^{-4}M	3 hrs	None	Reported as weakly positive	1. No dose-response. 2. Experiments were not repeated to confirm the positive finding.	Gasiorek and Bauchinger (1981)

(continued on the following page)

TABLE 4. (continued)

Test system	Duration of cultures	Cadmium compound	Dosage	Duration of treatment	Activation system	Results	Comments	Reference
Chinese hamster "Hy" cell line		Cadmium sulfate aqueous solution	10^{-4}M	1 hr and harvested at 2,4,6,8, 10,12,15,18, 21,24,27,30, days	None	Reported as positive	1. Colchicine-like effect 2. The type of sera has not been specified. 3. Protocol for chromosome preparation has not been specified.	Rohr and Bauchinger (1976)
Chinese hamster CHO cell line		Cadmium chloride in 0.1 MHCl	$2\text{x}10^{-6}$M	12, 24, 26, and 48 hrs	None	Reported as positive only in the presence of newborn calf (bovine) or human serum. Negative in the presence of fetal calf serum.	1. Threshold dosage was established as $1\text{x}10^{-1}$M for chromosomal aberration with newborn calf and human sera. 2. Classification of aberration types not given. 3. Active only in the presence of fetal calf serum.	Deaven and Campbell (1980)
Mouse mammary carcinoma FM3A		Cadmium chloride aqueous solution	$6.4\text{x}10^{-5}$M $3.2\text{x}10^{-5}$M $1.0\text{x}10^{-5}$M	24 and 48 hrs 24 and 48 hrs 24 and 48 hrs	None	Reported as negative	1. $6.4\text{x}10^{-5}$ too toxic. 2. Experiments were repeated to confirm the results.	Umeda and Nishimura (1979)

TABLE 5. MUTAGENICITY EVALUATION OF CADMIUM: IN VIVO CHROMOSOMAL ABERRATIONS IN HUMANS

Species	Number of exposed workers	Number of controls	Duration of exposure	Duration of culture (hrs)	Number of metaphases analyzed	Results	Comments	Reference
Human blood lymphocytes	14	5	3 months-26 years	48	2800 (exp) 900 (control)	Reported as negative	1. Sample size too small.	Dekundt et al. (1973)
Human blood lymphocytes	40	13	6 weeks-34 years	48	3740 (exp) 1243 (control)	Reported as negative	1. Study was conducted following good cytogenetic procedure.	O'Riordan et al. (1978)
Human blood lymphocytes	7, 12	6, 9	Not given	72	155/person	Reported as positive	1. The history of the patients, including exposure to other drugs, was not given in this paper.	Shiraishi and Yoshida 1972 Shiraishi 1975
Human blood lymphocytes from cadmium-exposed workers	5	3	5-24 years	48-72	100/person	Reported as negative	1. Sample size too small.	Bui et al. (1975)
Itai-Itai patients' blood lymphocytes	4	4		72	100/person	Reported as negative		
Human blood lymphocytes	24	15	3-6.5 years	48	4800 (exp) 1650 (control)	Reported as positive	1. The possibility of synergistic action of various metals cannot be ignored.	Bauchinger et al. (1976)

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TABLE 5. (continued)

Species	Source of cells	Cadmium compound	Dosage	Duration of treatment	Results	Comments	Reference
Mouse bone marrow	Bone marrow cells	Cadmium chloride	0.06% in diet	30 days	Reported as negative	1. Good technical procedure. 2. Data were anlyzed statistically.	Dekundt and Gerber (1979)
Mouse micronucleus	Bone marrow cells	Cadmium chloride	4 mg/kg/ day	5 days	Reported as negative	1. Number of mice per group was 3. 2. Number of polychromatic erythrocytes scored was 300 from each mouse.	Heddle and Bruce (1977)
Rat embryos	Embryonic cells	Kilhman virus Cadmium chloride			Reported as positive	1. Cadmium enhanced the effects of virus. 2. Cadmium alone was ineffective.	Zasukhina et al. (1977)
Mouse dominant lethals	Score dead proportion of implants in the uterus	Cadmium chloride	1.35, 2.7, 5.4 mg/kg	1 day	Reported as negative	1. Standard dominant lethal assay was performed. 2. The entire spermatogenic cycle was covered.	Epstein et al. (1972)

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TABLE 5. (continued)

Species	Source of cells	Cadmium compound	Dosage	Duration of treatment	Results	Comments	Reference
Mice dominant lethals	Score dead proportional implants in the uterus	Cadmium chloride	1.75 mg/kg	1 day	Reported as negative	1. All cell stages not sampled.	Gilliavod and Leonard (1975)
Mice (female) dominant lethals	Score dead and live implants in the uterus	Cadmium chloride	2 mg/kg	0.5 to 4.5 days	Reported as negative	1. Experiments repeated three times.	Suter (1975)
Mice heritable translocation	Testicular cells from F_1 males	Cadmium chloride	1.75 mg/kg	1 day	Reported as negative		Gilliavod and Leonard (1975)
Mice (male)	Spermatocytes	Cadmium chloride	0.5, 1.75, 3.0 mg/kg	90 days	Reported as negative		Gilliavod and Leonard (1975)
Mice (female)	Oocytes	Cadmium chloride	3 mg/kg 6 mg/kg	12 hrs	Reported as positive	1. Technical problems in processing oocytes not discussed.	Shimada et al. (1976)
Syrian hamsters (female)	Oocytes	Cadmium chloride	1, 2, 4 mg/kg	12 hrs	Reported as positive	1. Technical problems in processing oocytes not discussed.	Watanabe et al. (1979)
Mice (female)	Blastocysts	Cadmium chloride	1.5, 3.0 mg/kg	77 hrs	Reported as positive for aneuploidy		Watanabe and Endo (1982)

concentration of the compound was used, no dose-response relationship is available for this study. In addition, no information was given on the solvent used to dissolve the test compound, and the number of cells scored was small. For these reasons, and because no indication as to the reproducibility of the results was given, this study cannot be regarded as strong evidence for the cytogeneticity of cadmium.

Dekundt and Deminatti (1978) investigated the mutagenic effects of cadmium chloride in cultured human lymphocytes. They treated two batches of cell cultures and analyzed chromosomes as follows: One batch of cultures was treated at 0 hours and at 24 hours after the initiation of cell cultures with 5 x 10^{-5} and 5 x 10^{-6}M cadmium chloride. Chromosome preparations were made 48 hours after the initiation of the culture, using the standard air-drying technique. In cultures treated 0 hour after the initiation, one hundred metaphases were scored for each dose. There were 3% aberrations (1% aneuploidy, 2% gaps) at 5 x 10^{-5}M, and 7% aberrations (5% aneuploidy, 2% gaps) at 5 x 10^{-6}M. In cultures treated 24 hours after the initiation of cultures, there were 5% aberrations (1% aneuploidy, 4% gaps) at 5 x 10^{-5}M, and 2% aberrations (1% gaps and 1% fragments) at 5 x 10^{-6}M. The control aberration frequency was 5% (3% aneuploidy, 2% gaps). The other batch of cultures was treated at 0 hour and 24 hours, and chromosome preparations were made 72 hours after the initiation of cell cultures. One hundred metaphases were analyzed for aberration frequencies from each group. In cultures treated at 0 hour, there were 4% aberrations (3% aneuploidy, 1% gaps) at 5 x 10^{-5}M, and 3% aberrations (3% aneuploidy) at 5 x 10^{-6}M. Cultures treated after 24 hours of initiation exhibited 6% aberrations (2% aneuploidy, 1% fragment, 3% gaps) at 5 x 10^{-5}M, and 4% aberrations (1% aneuploidy, 2% gaps) at 5 x 10^{-6}M. The control frequencies were 1% aneuploidy and 1% gaps. The first batch of cultures exhibited aberration frequencies similar to the control levels. The second batch of cultures, treated only 24 hours after the initiation, exhibited aberration frequencies two to three times above the control levels. These aberrations occurred mostly in the form of aneuploidy and gaps. The significance of chromosomal gaps is not yet understood, and they may not represent true chromosomal aberrations because of their tendency toward restitution. Furthermore, the slight increase in the incidence of aneuploidy may be due to technical difficulties, such as the scattering of chromosomes during the preparation of slides, which tends to result in uneven distributions of cells.

Paton and Allison (1972) exposed human lymphocyte cultures and cultures of the established human cell lines WI38 and MRC5 to at least two concentrations (not specified) of cadmium chloride. The duration of treatment was 48 hours for lymphocytes and 24 hours for WI38 and MRC5. Chromosomal preparations from 100-200 cells were analyzed for aberrations. No aberrations were recorded in treated cells, but because the actual data from the experiment were not given, the study cannot be critically evaluated.

Gasiorek and Bauchinger (1981) exposed unstimulated human blood lymphocytes (G_0) in 1 mL quantities to 10^{-4}, 10^{-5}, 10^{-6}, 10^{-7}, and 10^{-8}M of cadmium acetate for 3 hours. The cells were washed free of cadmium acetate and grown in medium containing fetal calf serum and PHA for 48 hours at 37°C; chromosome preparations were made with the standard air-drying technique. Chromosome analysis of 200 cells per treatment indicated a dose-related increase in the incidence of chromosome gaps. The frequencies of gaps were 0.160, 0.115, 0.135, 0.085, and 0.055 per cell, respectively, for the above doses, as compared to the control frequency of 0.058 per cell. Data were analyzed by the Mann-Whitney rank U-test to compare the incidence of chromosome changes in different samples (significance taken as $P < 0.05$). The frequencies of structural aberrations (chromatid deletions and acentric fragments) were 0.025, 0.010, 0.005, 0.020, and 0.010 per cell, respectively, for the same doses, whereas in controls the frequency of structural aberrations was 0.005 ± 0.005 per cell. Analysis by Mann-Whitney rank U-test indicated that structural chromosome aberrations were significantly higher than in controls, although no dose-response relationship was evident. No metabolic activiation system was used. Sufficient numbers of metaphases (200 per dose) were scored, and a standard protocol was employed. Although these data suggest a mutagenic response, the lack of a dose-dependent response makes it important that the results of this experiment be confirmed in another study.

Studies on Rodent Chromosomes In Vitro

Rohr and Bauchinger (1976) studied the effects of cadmium sulfate in the Chinese hamster cell line "Hy" using three types of experiments. In a long-term experiment without recovery, cells were exposed to cadmium sulfate at concentrations of 10^{-8} to 10^{-5}M. Chromosome preparations were made following treatment of cells for 16 hours with 0.2 ug/mL of colecemid and hypotonic solution. The 16-hour time period was chosen in order to analyze the cells after exposure during a whole cell cycle. Because concentrations of 10^{-5}M were toxic to cells after 16 hours of exposure, chromosome analysis could not be made. In a short-term experiment without recovery, cells were treated only for 3 hours at a concentration range of 10^{-8} to 10^{-4}M, and chromosome preparations were made without the addition of colcemid and hypotonic solution. This experiment indicated a typical stathmokinetic effect (spindle inhibition) similar to that caused by colcemid. The mitotic index increased with higher concentrations of cadmium sulfate. In a short-term experiment with recovery, a concentration of 10^{-4}M was chosen, and cells grown on coverslips were exposed for 1 hour. Cells with coverslips were washed free of cadmium sulfate, transferred to fresh medium, and grown for 2 to 33 hours. Chromosome preparations were made at

2, 4, 6, 8, 10, 12, 15, 18, 21, 24, 27, 30, and 33 hours after the cells were transferred to the test medium. In all, 500 cells were scored for each recovery period. The incidences of aberrations (0.2 to 0.6% structural and 2.4 to 3.7% numerical) after 2 to 12 hours of recovery were similar to control levels (0.1% structural and 2.4% numerical). Between 15 and 21 hours, the structural aberrations ranged from 10.2% to 22.8%, and the numerical aberrations ranged from 3.0% to 4.9%. The aberration frequencies for the interval of 24 to 33 hours were lower than for the interval of 15 to 21 hours. During this period (24-33 hours), the structural aberrations ranged from 1.2 to 4.4%, and the numerical aberrations ranged from 7.8% to 10.8% (2.4% in controls).

The significance of this study is that cadmium was found to induce numerical chromosomal aberrations by interfering with spindle function. Numerical chromosomal aberrations have been well documented in many forms of cancers. Many chromosomally fragile syndromes, such as Fanconi's anemia, are predisposed for cancer induction.

Deaven and Campbell (1980) studied the effects of cadmium chloride on chromosomes in CHO cells grown in the presence of bovine serum and fetal calf serum. A concentration of 2×10^{-6}M cadmium produced 17, 26, 62, and 74% damaged cells, respectively, at 12-, 24-, 36-, and 48-hour analyses of metaphase chromosomes. However, the presence of fetal calf serum and 2×10^{-6}M cadmium chloride did not induce growth inhibition or chromosome aberrations. According to these investigators, fetal calf serum appeared to protect the cells from the damaging effects of cadmium, whereas newborn calf serum and human serum actively transported cadmium ions into the cell nuclei, thus damaging the chromosomes. These authors also examined the frequencies of sister chromatid exchanges (SCEs) in cells grown in F-10 containing 15% newborn calf serum at a concentration of 4×10^{-7}M cadmium chloride (low to marginal toxicity). The SCE rate was not elevated above control levels (10 SCEs/cell). The range of SCEs was 2 to 18 for cadmium-treated cells, and the range for controls was 4 to 19 per cell. This study is assessed as inconclusive for the reason that the exact role of serum in causing chromosome aberrations is still not known. The importance of these data resides in the fact that virtually all other studies have failed to consider the potential importance of the choice of serum in such experiments.

Umeda and Nishimura (1979) investigated the clastogenic effects of cadmium chloride in FM3A cells derived from C3H mouse carcinoma. Cells were grown in Eagles minimal essential medium supplemented with 10% bovine serum. Cells were exposed to 6.4×10^{-5}, 3.2×10^{-5}, and 1.0×10^{-5}M of aqueous cadmium chloride. After 24 and 45 hours of exposure, chromosome preparations were made and analyzed. One hundred metaphases were scored for each dose. No significant increase in the aberration frequency was noted in treated cultures as compared to control cultures. There were no metaphases in cells treated with 6.4×10^{-5}M either at 24 hours or at 48 hours--an indication of toxicity. At 3.2×10^{-5}M the aberration frequencies were 2% and 3%, at 24 and 48 hours respectively. At the lowest concentration of 1.0×10^{-5}, the aberration frequencies were 1% each for the 24- and 48-hour treatments. The control cultures exhibited 2% aberrations at 24 hours and 1% aberrations at 48 hours. Experiments were performed using accepted procedures. Three concentrations of the test compound were used, and 100 metaphases were scored for evaluation.

Zasukhina et al. (1977) reported increased aberration yields in rat embryos exposed to virus and cadmium chloride. Rat embyro cultures were infected with Kilhman virus, and cadmium chloride (3.5×10^{-6}M) was then introduced into the cell cultures. Chromosome preparations were performed 24 hours after the infections. Examination of metaphase cells revealed a 10% aberration rate as compared to a rate of 2% in controls. In control cultures infected with virus only, the aberration frequency was 6%, and in cultures treated with cadmium chloride only, the aberrations frequency was 3%. These results indicate that cadmium chloride enhances virus-induced chromosomal aberrations. The researchers also studied the effect of cadmium chloride on DNA; they reported cadmium chloride-induced degradation with evidence for induction of nonreparable DNA synthesis.

Studies on Human Chromosomes In Vivo

Shiraishi and Yoshida (1972) and Shiraishi (1975) obtained markedly positive results from Japanese Itai-Itai patients. The Itai-Itai disease is believed to be induced by cadmium contamination. Analysis of blood lymphocytes from 72-hour cultures derived from these patients exhibited a high rate of chromosomal aberrations (26.7%) compared to the aberration rate in controls (2.6%). Blood cadmium levels were not given. The exposure parameters used in this study are presented in Table 5.

The results obtained by Shiraishi and Yoshida (1972) and Shiraishi (1975) contradicted the results obtained by Bui et al. (1975), who performed chromosomal analysis in four Itai-Itai patients (blood cadmium level 15.5-28.8 ng/g), five Swedish workers exposed to cadmium (blood cadmium level 24.7-61 ng/g), four Japanese controls (blood cadmium level 4.4-6.1 ng/g), and three Swedish controls (blood cadmium level 1.4-3.2 ng/g). The incidences of aberrations after 72 hours of culture were 2.3% numerical and 6.6% structural aberrations in the Itai-Itai patients, as compared with the Japanese controls, in which frequencies of 4.5% numerical and 6.0% structural aberrations occurred--a finding which indicates that no differences existed between the controls and the Itai-Itai patients. In the five Swedish workers exposed to cadmium, chromosomal aberration incidences were 1.0% numerical and 2.0% structural aberrations, while in the three Swedish controls the frequencies were 0.7% numerical and 4.7% structural aberrations, indicating nonmutagenic responses.

The discrepancy between the results of Shirashi and Yoshida (1972) and Bui et al. (1975) in Itai-Itai patients could possibly be due to factors other than exposure to cadmium chloride, such as the time of initiation of cultures after the blood was drawn. In the experiment of Bui et al., the subjects were not exposed to drugs and X-rays, nor did they suffer from viral infections at the time of venipuncture. These factors were not controlled for in the study by Shirashi and Yoshida.

Dekundt et al. (1973) investigated the incidence of chromosomal aberrations in 14 workers who had been exposed to zinc, lead, and cadmium in a zinc smelting plant. The workers were classified into three groups based on degree of exposure. Group 1 consisted of five workers who had been exposed to high levels of zinc (concentrations not specified), low levels of lead (1% w/w of the mineral), and cadmium (concentration negligible). Group 2 consisted of five workers who had been exposed to dust containing high levels of all three metals: zinc (concentration not specified), lead (4% w/w), and cadmium (1% w/w). Group 3 consisted of four workers who had been exposed to mud and dust containing high levels of lead (60% w/w) and cadmium (1% w/w). The control group consisted of three normal individuals. Chromosomal analysis from blood lymphocytes cultured for 72 hours indicated 3.87%, 1.6%, and 2.76% aberrant cells, respectively, in groups 1, 2, and 3, while the control frequency was 1.55%. Since the incidence of aberrations in group 3 was less than that in group 1, it does not appear that cadmium contributed to the frequency of aberrations in this study. The authors' analysis of their data using the t-test also indicated that cadmium exposure did not induce a significant increase in the frequency of aberrations. Blood cadmium levels were not determined in this experiment.

Bauchinger et al. (1976) studied 24 workers (25-53 years of age) exposed to lead (mean blood lead level 1 ± 7 ug/100 mL) and cadmium (mean blood cadmium level 0.40 ± 0.27 ug/mL). The workers were exposed to these metals for approximately 3 to 6.5 years at a smelting plant. Of the 4,800 metaphases scored from lymphocytes cultured for 48 hours, an increase in both chromosomal and chromatid-type aberrations (1.354 ± 0.994%) was noted, in comparison with an aberration frequency of 0.467 ± 0.916% in 1,650 metaphases derived from 15 controls (mean blood cadmium level 0.15 ug/mL). The authors point out that "the observed chromosome aberrations cannot be causally related to cadmium because the workers were also exposed to lead and zinc." Dekundt and Leonard (1975) reported a significant ($P < 0.02$) increase in the incidence of "complex chromosomal aberrations" in a group of 23 men exposed to high levels of cadmium and lead (23.5 to 75.9 ug/100 mL), as compared with controls.

O'Riordan et al. (1978) studied chromosomal aberrations in blood lymphocytes from 40 workers exposed to cadmium salts (chemical names not specified, mean blood cadmium level 1.95 ug/100 mL range < 0.2 to 14.0 ug/100 mL) for a period of 6 weeks to 34 years. In 3,740 cells examined from these workers, four chromatid interchanges were observed. In the control population of 1,243 cells derived from 13 normal subjects (mean blood cadmium level less than 0.2 ug/100 mL in 8 donors and 0.6 to 2.9 ug/mL in 5 donors), no aberrations were observed. Since data were pooled from all of the 40 workers studied, it is not clear whether the four chromatid interchanges came from one exposed worker or from more than one worker. The occurrence of chromatid exchanges, though small in number (4/3,740 cells), does not necessarily indicate a negative response, but does indicate that the study should be considered inconclusive.

Most of these studies of smelting plant workers reflect mixed exposures to cadmium and to other metals such as zinc, lead, chromium, and nickel. Since smelters commonly process relatively crude materials, exposure to these other metals cannot be eliminated as possible contributors to the observed effects.

Studies on Rodent Chromosomes In Vivo

Dekundt and Gerber (1979) investigated the in vivo cytogenetic effects of cadmium chloride (3.27×10^{-7}M, 0.06%) in mice. Mice were maintained on a standard diet (1.1% calcium) or on a low-calcium diet (0.03%) for one month. In both cases the diet was supplemented with cadmium chloride. Cadmium chloride did not induce chromosomal aberrations in bone marrow cells significantly above the control level either in the normal or in the low-calcium diet groups. The frequency of aberrations in animals treated with cadmium chloride that were given the standard diet (1.1% calcium) was 2.20%, and the frequency in animals treated with cadmium chloride that were given the low calcium diet (0.03%) was 1.60%. The control frequencies were 1.8% and 2.0%, respectively. The results indicate that cadmium chloride does not induce chromosomal aberrations in mice by this route of exposure.

Micronucleus Assay

The micronucleus assay is based on the fact that chromosome fragments induced by mutagenic chemicals are unable to segregate normally due to lack of centromeres during cell division, and form small nuclei or micronuclei in daughter cells. Heddle and Bruce (1977) studied the ability of cadmium chloride to induce micronuclei in the mouse. Three groups of mice (F_1 of C57BL/6X C3H/He), each group containing three animals, were given daily intraperitoneal injections of cadmium chloride for 5 days with total doses of 1, 6, and 16 mg/kg, respectively. Mice were sacrificed, bone marrow smears were prepared, and 333 polychromatic erythrocytes from each mouse were scored for the presence of micronuclei. No increase in the incidence of micronuclei was observed. In this study, 1,000 cells were analyzed for each dose group (333 cells from each of 3 mice). The spontaneous frequency of micronuclei was 0.5%. An observation of 1% over the control value was considered a positive response. According to these authors, the frequency of micronuclei in the experimental groups did not differ from the control level. These results are presently considered to be inconclusive. The data should be confirmed with larger numbers of animals (10 per dose group) and analyses of at least 2,000 polychromatic erythrocytes per dose group.

Dominant Lethal Assay

The ability of cadmium chloride to induce dominant lethal mutations, which result in the death of fetuses during various stages of development, has been investigated (Epstein et al. 1972; Gilliavod and Leonard 1975; Ramaiya and Pomerantseva 1977; Suter 1975; Sutou et al. 1980 a, b).

Epstein et al. (1972) evaluated the dominant lethal effects of cadmium chloride in ICR/Ha mice. Groups of seven or nine male mice, 8 to 10 weeks of age, were injected intraperitoneally with 1.35, 2.7, 5.4, and 7.0 mg/kg of cadmium chloride in distilled water. Treated males were bred with virgin females 8 to 10 weeks of age. Each male was allowed to mate with three virgin females per week for 8 weeks. Mated females were sacrificed on the 13th day and analyzed for dead (dominant lethals) and live implants. According to these authors, cadmium chloride did not induce a statistically signficant increase in dominant lethal mutations over the control value. This study sampled all germ cell stages, spermatozoa, spermatids, spermatocytes, and spermatogonia.

Gilliavod and Leonard (1975) investigated the dominant lethal effects of cadmium chloride in another strain of mice, BALB/c. One dose of 1.75 mg/kg cadmium chloride was injected into male mice (11-13 weeks of age) through the intraperitoneal route. The treated males were bred with three virgin females every week for 3 weeks. The mated females were sacrificed on the 10th day, and the number of corpora lutea and dead and live implants were counted and compared with controls. No dominant lethal effects were observed in treated or control groups.

These investigators treated the parent male mice with only one acute dose of the test compound. Furthermore, they bred the treated males with normal females for only 3 weeks, which is too short a period of time in which to sample stages of spermatogenesis. The standard method of performing a dominant lethal test is to breed the treated males for 8 weeks. For the above reasons, this report is judged to be inconclusive.

Suter (1975) studied the mutagenic effects of cadmium chloride using the dominant lethal assay in female mice (F_1 progeny of C_3H and C57BLA). According to this investigator, cadmium chloride had no dominant lethal effects in female mice. Female mice of the F_1 (10 x C_3H) stock were injected intraperitoneally with 2 mg/kg cadmium chloride, exposing the germ cells (oocytes) at the dictyate stage of development, and were bred with untreated males for 0.5 to 4.5 days post-injection. Mated females, as evidenced by the vaginal plug, were sacrified 12-15 days later, and the numbers of corpora lutea, total implants, living implants, and percent of dead implants per female were determined. No differences were noted between the treated and control groups. In the treated group, the frequencies of corpora lutea, total implants, living implants, and dead implants per female were 8.2, 7.8, 6.9, and 6.9% respectively, as compared to control frequencies of 7.6, 6.8, 6.4, and 6.1% per female.

Ramaiya and Pomerantseva (1977) investigated the mutagenic effect of cadmium chloride using the dominant lethal test. F_1 hybrid mice (CBA x C57BL) aged 2.5 to 3 months were selected for these studies. Males were given a single intraperitoneal injection of aqueous cadmium chloride solution. Three doses, 1.0, 2.0, and 4 mg/kg, were employed. LD_{50} was determined to be 6.9 mg/kg. Treated males were mated with untreated females for a period of 6 weeks, covering the entire spermatogenic cycle. Dominant lethals, as noted by preimplantation and postimplantation losses and the ratio between the dead and live implants, were recorded. No significant ($P > 0.01$) increases in the dominant lethal frequencies were recorded. These results are regarded as negative since the authors followed appropriate protocols, the dosage selection was based on LD_{50}, and the data were analyzed statistically.

From the above studies it appears that cadmium chloride has no mutagenic potential as measured by the mammalian dominant lethal test. However, the exact nature of the damage that results in dominant lethal effects is not known. The mammalian dominant lethal test is not considered to be a sensitive test for detecting all types of mutagens (Russel and Matter 1980) because of the high spontaneous levels of dominant lethal events that occur during development.

Heritable Translocation Assay

Gilliavod and Leonard (1975) evaluated the mutagenic effects of cadmium chloride in BALB/c mice using the F_1 heritable translocation assay. Male mice (number not specified) were treated with 1.75 mg/kg of cadmium chloride intraperitoneally, and each treated male was bred with three untreated virgin females once weekly for 3 weeks. The spermatocytes of the resulting 120 F_1 male progeny were analyzed for the presence of heritable chromosomal translocation by standard cytogenetic methods. No evidences of heritable translocation were noted in the spermatocytes of F_1 males. This portion of the study is regarded as inconclusive for the following reasons: Only a single concentration of cadmium chloride was used; treated males were mated for only 3 weeks instead of for 8 weeks; and no experimental controls were used.

Gilliavod and Leonard (1975) also investigated the mutagenic effects of cadmium chloride in BALB/c mice using the spermatocyte assay. Males in groups of 10 were treated with 0.5, 1.75, and 3.0 mg/kg of cadmium chloride intraperitoneally. After 3 months, treated males were sacrificed and spermatocytes (100 cells per animal) in the testes were analyzed for translocations that may have been passed on from treated spermatogonia. No translocations were found in either treated or control animals. The spermatocyte assay is not a very sensitive test and is not commonly employed in mutagenicity tests; therefore this portion of the Gilliavod and Leonard (1975) study is also regarded as inconclusive.

Chromosomal Nondisjunction (Aneuploidy) in Whole Mammals

The effects of cadmium chloride on oocytes of mice (Shimada et al. 1976), on oocytes of Syrian hamsters (Watanabe et al. 1979), and on spermatocytes of mice (Gilliavod and Leonard 1975) have been investigated.

Shimada et al. (1976) induced superovulation by injecting female mice, ddy strain, with 5 international units (iu) of pregnant mare's serum (PMS) followed 48 hours later by 5 iu of human chorionic gonadotrophin (HCG). Mice were given 3 mg/kg or 6 mg/kg of cadmium chloride 3 hours after the administration of HCG, and were dissected 12 hours after the cadmium chloride administration. Chromosome preparations were made from unfertilized oocytes at the second meiotic metaphase, using the method described by Tarkowski (1966). No structural chromosome abnormalities were found. However, numerical aberrations (aneuploidy) were found to be statistically significant ($P = 0.015$) in the dose group of 3 mg/kg group as compared to controls. The authors postulated that this nondisjunction may be due to the spindle-inhibiting effects of cadmium.

Watanabe et al. (1979), using Syrian hamster oocytes and cadmium chloride, reported even more pronounced incidences of aneuploidy. Cadmium chloride at concentrations of 1.0, 2.0, and 4 mg/kg was injected subcutaneously to groups of 20 female Syrian hamsters 5 hours before ovulation. Matched controls were given equal volumes of normal saline. Females were sacrificed 12 hours after the treatment, and the oocytes were recovered from the ampulla. Analysis revealed that 6 females out of 20 from the 1.0 mg/kg group, 11 females out of 20 from the 2.0 mg/kg group, and 12 females out of 20 from the 4.0 mg/kg group had numerical chromosomal abnormalities, such as hyperhaploidy and diploidy in oocytes, as compared to 3 out of 20 in control females. The results were statistically significant ($P < 0.05$ and $P < 0.01$) in the treated groups as compared to the control group. Cadmium-treated animals were also analyzed for cadmium accumulation in the ovary, using atomic absorption spectrophotometry. The results indicated statistically significant ($P < 0.05$) increases in the accumulation of cadmium in the ovaries of treated females as compared to control females. Both of these results appear to indicate a positive response of cadmium in inducing numerical chromosomal abnormalities in mammalian oocytes.

Watanabe and Endo (1982) analyzed the chromosomes of the blastocysts from mice treated with cadmium at the metaphase 1 stage of oogenesis to determine the effects of cadmium from the oogenesis stage to the preimplantation stage. Female virgin mice of 8-12 weeks of age were induced to superovulate by administering 5 iu of pregnant mare's serum (PMS) followed in 48 hours by 5 iu of of human chorionic gonadotrophin (HCG). Three hours after HCG administration, the animals were injected subcutaneously with 1.5 mg or 3.0 mg/kg body weight of cadmium chloride. Shortly after the treatment with cadmium chloride, they were mated with males of the same age group. About 80 hours after mating, the females were injected intraperitoneally with 4.0 mg/kg of colchicine, and

2 hours later the animals were sacrificed, blastocysts from the uterus were placed into Hanks' balanced salt solution, and chromosome preparations were made. Aneuploid cells were found in 8 out of 65 blastocysts from the group treated with 1.5 mg/kg of cadmium, and 10 out of 63 blastocysts from the group treated with 3.0 mg/kg of cadmium, indicating that chromosomal nondisjunctions induced in oocytes are transmitted to embryos. In the control group, aneuploidy was found in 2 blastocysts out of 59.

All of the above studies strongly indicate that cadmium acts mutagenically to alter the number of chromosomes through spindle inhibition. The concentrations of cadmium used in these studies were similar to those that have been used in cancer bioassays. Supporting evidence that another metal induces chromosomal nondisjunction can be obtained from studies of methyl mercury in Drosophila melanogaster (Ramel and Magnusson 1979) and in Syrian hamsters (Mailhes 1983). The occurrence of aneuploidy is well documented in cancer cells. Many chromosomally fragile syndromes, such as Fanconi's anemia, ataxia telangiectasia, and Bloom's syndrome, have been known to be predisposed for cancer induction. Colchicine, the well-known spindle inhibitor, has been used clinically for the treatment of gout. There have been reports that these patients carry numerical chromosomal abnormalities in their blood lymphocytes (Ferreira and Buoniconti 1968). Epidemiological studies at the National Cancer Institute (Dr. Robert Hoover, personal communication) are presently being conducted to determine the susceptibility of these types of patients to cancer.

Sperm Abnormality Assay in Mammals

Heddle and Bruce (1977) evaluated the effects of cadmium by means of the sperm abnormality assay. The sperm abnormality assay is based on the observation of increased incidence of sperm heads with abnormal shapes as a result of exposure to chemical mutagens (Wyrobek and Bruce 1975). Three groups of mice of the genotype (C57BL/6 x C3H/He)F_1, each consisting of three mice, were given daily intraperitoneal injections of cadmium chloride for 5 days with doses of 1, 4, and 16 mg/kg, respectively. After sacrifice of the animals by means of cervical dislocation, sperm suspensions were made from sperm collected from the cauda epididymis. The sperm suspensions were stained with 1% eosin-Y in water, and smears were dried and mounted under coverslips. One thousand sperm heads were evaluated for morphological abnormalities. The background frequency of sperm head abnormalities in the control populations was 1%. Under the conditions of the test, no increases in sperm head abnormalities were observed in the treated group as compared to controls.

CHROMOSOMAL ABERRATIONS IN PLANTS

Levan (1945) reported that treatment of Allium cepa root-tips with cadmium chloride induced C-mitosis. This observation was later confirmed by Avanzi (1950), using cadmium chloride concentrations ranging from 2 x 10^{-6}M to 5 x 10^{-2}M. Oehlkers (1953) reported that cadmium nitrate induced chromosomal aberrations in Vicia faba. Van Rosen (1953, 1954) reported the genotoxicity of cadmium as evidenced by chromosomal aberrations in the root-tips of plants such as Allium cepa, Beta vulgaris, Pisum abysinnicum, and Vicia sativa. Similar observations were made by Degraeve (1971) in Horedeum sativum and by Ruposhev and Garina (1977) in Crepis capillaris. Aberrations reported in these studies were of both chromatic and chromosomal types, with dose-related responses. Since many of these studies were published in foreign languages, the present report utilizes a summary derived from the review article published by Degraeve (1981).

BIOCHEMICAL STUDIES INDICATIVE OF MUTAGENIC DAMAGE

Some information is available on the effects of cadmium on animals, and although this information cannot, strictly speaking, be considered mutagenicity test data, it may be useful in evaluating the ability of cadmium to reach and damage the gonads. Dixon et al. (1976) reported that cadmium chloride at 2.24 mg/kg, administered intraperitoneally, caused damage to rat testes. A single 10 mg/kg intraperitoneal injection caused selective destruction of rat testes. Cadmium chloride, when administered intraperitoneally at 1 mg/kg, reduced the fertility of male mice at all sperm cell stages except that of spermatozoa (Lee and Dixon 1973). However, single oral doses up to 25 mg/kg had no effect on the fertility of male rats (Dixon et al. 1976), and cadmium chloride at 0.1 mg/L in drinking water for up to 90 days had no effect on the fertility of male rats. Intraperitoneal injection of cadmium chloride at 1/mg/kg decreased the incorporation of thymidine into spermatogonia in mice (Lee and Dixon 1973). These authors also observed the binding of cadmium to late spermatids *in vivo* and *in vitro*. Friedman and Staub (1976) studied the effects of cadmium chloride on DNA synthesis in Swiss mice. Cadmium chloride at 10 mg/kg inhibited DNA synthesis significantly. An aqueous solution of cadmium chloride was injected intraperitoneally at the above dose into five male mice, and the mice were sacrificed 3.5 hours later. Thirty minutes prior to sacrifice, mice were injected with 10 uCi [^{3}H] thymidine. Controls received only 10 uCi [^{3}H] thymidine. Testes were removed following cervical dislocation, DNA was isolated, and the specific activity was determined. Cadmium chloride was found to induce a statistically significant ($P < 0.01$) inhibition of [^{3}H] thymidine uptake (1.90 ± 0.58) in the testes as compared to controls (7.45 ± 1.44).

Mitra and Bernstein (1977, 1978) reported that when *E. coli* cultures were exposed to 3×10^{-6}M cadmium (Cd^{2+}), 82 to 95% of the cells lost their ability to form colonies on agar plate. Analysis of DNA strands from cells treated with various doses of Cd^{2+} indicated that there was a dose-related increase in the breakage of single-strand DNA. These investigators believe that the loss of viability in cadmium-treated cells is due to the single-strand DNA breakage. Cadmium-treated cells recovered viability when grown in Cd^{2+}-free liquid medium containing 10 mM hydroxyurea.

Sirover and Loeb (1976) investigated the infidelity of DNA synthesis brought about by cadmium chloride and cadmium acetate. Their assay measured the perturbation in the fidelity of DNA synthesis in vitro caused by soluble metal salts. Cadmium chloride and cadmium acetate were found to decrease the fidelity of DNA synthesis. Cadmium chloride has also been found to induce concentration-dependent inhibition of RNA synthesis (Hoffman and Niyogi 1977).

SUMMARY

Cadmium has been investigated for mutagenic activity in both prokaryotic and eukaryotic systems. Gene mutation studies in Salmonella typhimurium and E. coli have produced inconclusive results. However, cadmium in concert with MNNG induced dose-related increases in both reverse and forward mutations in Salmonella typhimurium. In yeast, gene mutation studies have also been inconclusive. In three gene mutation studies (in mammalian cell cultures, mouse lymphoma cells, and Chinese hamster lung and ovary cells) weak mutagenic responses to cadmium were observed. In another gene mutation study, which used mammalian cell cultures, dose-related increases in mutation frequency were obtained, indicating that cadmium is mutagenic.

Rec-assay in Bacillus subtilis resulted in a weak mutagenic response. In the Drosophila sex-linked recessive lethal test, cadmium was found to be nonmutagenic. However, the negative response in this study may have been due to inadequate test controls. The dominant lethal test in Drosophila resulted in a positive response with a dose-response relationship.

The results of chromosomal aberration studies in human lymphocytes and human cell lines treated with cadmium have been conflicting and contradictory. In Chinese hamster cells, chromosomal aberrations were noted following treatment with cadmium; however, in mouse carcinoma cells, no aberrations were recorded in response to cadmium treatment. In rodents, treatment with cadmium induced no chromosomal aberrations or micronuclei in bone marrow cells. Similarly, no dominant lethal mutations were noted in mice treated with cadmium. Chromosomal aberrations and gene mutations in plants exposed to cadmium have also been recorded.

The evidence that cadmium is a mutagen that interferes with spindle formation comes from both in vitro and in vivo studies in mammals. In in vitro studies using the Chinese hamster cell line "Hy," cadmium induced a stathmokinetic (spindle-inhibitory) effect similar to that of colchicine, which is a known spindle poison. Cadmium also was found to increase numerical chromosome aberrations (aneuploidy) in these cells. Similar and more significant results were obtained in studies on aneuploidy in whole mammals. In female mice and Syrian hamsters, cadmium induced chromosomal nondisjunction leading to aneuploidy in germ cells. A recent study demonstrated that the numerical aberrations induced by cadmium chloride in female germ cells of mice are inherited in the embryos.

The results of gene mutation studies in mammalian cell cultures, rec-assays in bacteria, chromosomal nondisjunction studies in cultured mammalian cells and intact mammals, chromosomal aberration studies in plants, and biochemical studies indicative of mutagenic damage, together with the synergistic effect in Salmonella and rat embryo cultures, support the conclusion that cadmium is mutagenic.

CARCINOGENICITY

Much of the evidence for the carcinogenicity of cadmium has been reviewed critically in earlier documents (IARC 1973, 1976; U.S. EPA 1977, 1981; Sunderman 1977, 1978; Hernberg 1977). This section updates findings mentioned previously and discusses recent findings not mentioned in earlier reviews.

ANIMAL STUDIES

Inhalation Study in Rats

A carcinogenicity study of cadmium administered to male Wistar rats by inhalation was reported by Takenaka et al. (1983). The animals were placed in a 225-liter inhalation chamber for exposure to cadmium chloride ($CdCl_2$) aerosol. Aerosol was generated by atomizing a solution of $CdCl_2$, and airflow through the atomizer was 0.7 L/min. Analytical measurements of cadmium levels were made by collecting aerosol samples in membrane filters in the intake and exhaust of the inhalation chamber. The data in Table 6 show that measured and nominal cadmium levels were quite close. An aerosol centrifuge was used to estimate particle size distribution. Aerodynamic mass median diameters were 0.55 um with an arithmetic standard deviation of 0.48 um.

TABLE 6. NOMINAL AND MEASURED CADMIUM CONCENTRATIONS OF CADMIUM CHLORIDE AEROSOLS USED FOR INHALATION (Takenaka et al. 1983)

Nominal concentrations	ug/m^3	50.0	25.0	12.5
Measured concentrations	ug/m^3	50.8	25.7	13.4
Standard deviation	ug/m^3	5.9	3.6	2.1
Number of measurements	--	212	220	210

The animals were initially 6 weeks old and weighed 133 to 135 g. For 18 months, 40 rats per group were continuously exposed to cadmium concentrations of 12.5 ug/m^3, 25 ug/m^3, and 50 ug/m^3. A control group of 41 rats received filtered air during the same period. Following the treatment period, the animals were allowed to survive for an additional 13 months until sacrifice. Body weights were recorded every 3 months during the entire study period. Decedents and survivors were necropsied, and tissues and organs were removed for histopathologic examination. Skulls were decalcified for pathologic evaluation. Samples of liver, lung, and kidney were digested in acid for estimation of cadmium content by atomic absorption spectroscopy.

Differences in body weights (Table 7) and mean survival times (Table 8) among control and treated animals were not statistically significant ($P > 0.05$).

A dose-related increase in the incidence of primary lung carcinomas in treated animals was evident, as shown in Table 8. The first epidermoid carcinoma and the first adenocarcinoma were found at 20 and 22 months, respectively, after treatment commenced. Several treated rats also develped adenomas and nodular hyperplasia in the lung. Metastases to the regional lymph nodes and the kidneys and invasion into the regional lymph nodes and the heart occurred in some rats with lung carcinomas. No lung tumors were found in control animals.

Nonneoplastic lesions and various tumors in other organs were found in both control and treated animals. None of these additional tumor types and nonneoplastic lesions was significantly ($P > 0.05$) different among the four groups.

The data in Table 9 show that cadmium was retained in the lungs, livers, and kidneys of survivors for as long as 13 months after cessation of exposure. Analysis of these tissues indicated that cadmium was absorbed and circulated throughout the body and that, although the lung was the target organ for carcinogenicity, the kidney retained the largest amounts of cadmium. Increases in cadmium

TABLE 7. AVERAGE BODY WEIGHTS OF RATS EXPOSED TO CADMIUM CHLORIDE
(Takenaka et al. 1983)

Exposure groups	Average body weights (months after the beginning of the inhalation)					
	0	3	7	10	12	15
Control	135.2[a] (4.8)	333.3 (27.4)	385.2 (30.5)	411.6 (31.2)	422.9 (31.7)	425.1 (31.8)
12.5 ug/m^3	135.1 (6.6)	320.9 (29.4)	375.3 (37.1)	405.2 (39.4)	417.2 (41.4)	420.0 (38.8)
25 ug/m^3	133.4 (6.7)	326.6 (28.6)	382.1 (32.1)	410.0 (32.8)	425.7 (35.9)	428.3 (36.1)
50 ug/m^3	133.3 (6.7)	323.5 (29.0)	375.1 (32.2)	403.2 (34.8)	417.0 (36.6)	422.0 (38.5)
	18[b]	21	24	27	30	
Control	434.9 (32.4)	428.2 (31.4)	406.2 (41.3)	405.7 (31.3)	367.3 (39.8)	
12.5 ug/m^3	424.6 (41.0)	421.8 (41.2)	409.5 (45.9)	408.5 (40.9)	372.5 (41.8)	
25 ug/m^3	437.6 (38.1)	441.2 (37.7)	429.2 (45.9)	423.9 (37.6)	375.4 (47.8)	
50 ug/m^3	424.3 (40.6)	424.9 (43.8)	415.2 (42.6)	398.4 (35.8)	357.8 (41.5)	

[a] Mean value (± S.D.).
[b] End of the inhalation.

TABLE 8. SURVIVAL TIMES AND LUNG CHANGES OF WISTAR RATS AFTER EXPOSURE TO CADMIUM CHLORIDE AEROSOLS
(Takenaka et al. 1983)

				Incidence of lung adenomas and carcinomas						
						Carcinomas				
Exposure groups	Initial no. of rats	Survival time in weeks mean value $\pm$ S.D.	No. of rats examined histologically	Adenomatous proliferation	Adenomas	adeno-	epidermoid	combined adeno- and epidermoid	mucoepidermoid	Total (%)
Control	41	122 ± 19	38[a]	1	0	0	0	0	0	0
12.5 ug/m^3	40	119 ± 17	39[b]	6	1	4	2	0	0	6(15.4%)[e]
25 ug/m^3	40	125 ± 15	38[c]	5	0	15[f]	4	1	0	20(52.6%)[f]
50 ug/m^3	40	116 ± 23	35[d]	3	1	14[f]	7	1	3	25(71.4%)[f]

[a] Two rats died during the first 18 months; another rat was not examined because of autolysis.
[b] One rat was not examined because of autolysis.
[c] Two rats were not examined because of autolysis.
[d] Three rats died during the first 18 months; two other rats were not examined because of autolysis.
[e] P = < 0.01.
[f] $P < 1.0 \times 10^{-5}$.

TABLE 9. CONCENTRATIONS OF CADMIUM IN LUNGS, LIVER, AND KIDNEYS OF RATS EXPOSED TO CADMIUM CHLORIDE FOR 18 MONTHS (13 MONTHS AFTER THE END OF THE INHALATION) (Takenaka et al. 1983)

Exposure groups	No. of rats	Cadmium concentrations (ug/g wet weight)		
		Lungs	Livers	Kidneys
Control	9	0.03	0.1 ± 0.1[a]	0.3 ± 0.1
12.5 ug/m^3	6	5.6 ± 1.0	2.2 ± 0.6	13.5 ± 3.2
25 ug/m^3	9	4.7 ± 1.5	5.9 ± 1.5	16.4 ± 3.6
50 ug/m^3	9	10.4 ± 4.2	13.5 ± 3.0	33.6 ± 10.7

[a] Mean value ± S.D.

levels were dose-related in liver in all treatment groups and in lung and kidney in the mid-dose and high-dose groups. Pathologic changes apparently were not observed in kidney and liver, thus suggesting that the cadmium levels found did not have a toxic effect in these tissues.

The authors attributed their success in demonstrating the carcinogenicity of cadmium to: 1) performance of a long-term study using $CdCl_2$ aerosols that were retained at a rather high level in the lungs after cessation of exposure, and 2) continuous observation of the animals over an extended duration (31 months). Most of the lung carcinomas were detected after the 27th month of the study.

In a pilot study in the same laboratory, four adenomas and one adenocarcinoma were found in 10 rats after 18 months of exposure to a $CdCl_2$ aerosol (20 ug/m^3). There was no observation period after the 18-month exposure (Heering et al. 1979). These results fit well with the data obtained in the more detailed study conducted by Takenaka et al. (1983).

In a recent investigation, Greenspan and Morrow (1984) showed that exposure of rats to an aerosol of $CdCl_2$ at 5 mg Cd/m^3 for 30 minutes reduced the number of particles phagocytized by the lung macrophages for up to 8 days. At an airborne concentration of 1.5 mg Cd/m^3 the phagocytization of particles was stimulated. The adhering properties of the phagocytes were reduced at both exposure concentrations for as long as 12 days. The potential of $CdCl_2$ for altering the normal phagocytic activity could explain why Takenaka et al. (1983) were able to produce such a marked carcinogenic response.

In an earlier study, Hadley et al. (1979) reported one lung tumor among 34 male Wistar rats one year after they had been exposed to 60 ug/L of cadmium oxide (CdO) for 30 minutes. While this regimen was not adequate for a determination of carcinogenicity, it is noteworthy that the authors of the study observed testicular alterations after this treatment. They pointed out that these changes occurred at doses lower than the minimum effective dose required to induce degeneration with soluble cadmium salts given parenterally if no more than a 20% pulmonary retention is assumed (1.5 u moles Cd/kg for inhalation versus 5-10 u moles Cd/kg).

Oberdoerster et al. (1979) compared the lung clearance of CdO and $CdCl_2$ after a 45-minute exposure to airborne concentrations of 930 ug/m^3 and 760 ug/m^3, respectively. The aerodynamic mass medium diameters were 0.38 and 0.46 um for $CdCl_2$ and CdO, respectively. Despite the differences in chemical solubility, the long-term clearances were equal. The only difference was that cadmium was cleared more rapidly in the first eight days after exposure. The authors suggested that this might be due to bronchial clearance mechanisms for the less soluble CdO particles.

Intratracheal Studies in Rats

Sanders and Mahaffey (1984) evaluated the carcinogenicity of CdO in male Fischer 344 rats. Four groups of 46 to 50 rats each were treated as follows: Group 1 (untreated controls) received one intratracheal instillation of 0.9% sodium chloride solution (the dosing vehicle); Group 2 was given an intratracheal instillation of 25 ug CdO when 70 days old; Group 3 received intratracheal instillation of 25 ug CdO when 70 and 100 days old for a total dose of 50 ug; Group 4 was given intratracheal instillations of 25 ug CdO when 70, 100, and 130 days old for a total dose of 75 ug. The authors stated that the 25-ug dose was 75% of the LD_{50} by the route of administration used. Instilled CdO had a count median diameter of 0.5 um. The animals were allowed to survive until spontaneous death. All animals were necropsied, organs were weighed, and tumors, lesions, and major tissues and organs from all of the rats (except 12 lost due to autolysis or cannibalism) were examined histopathologically.

Median survival times were 793, 824, 785, and 788 days for Groups 1, 2, 3, and 4, respectively. Survival times and organ weights (body weights were not obtained) were similar ($P > 0.05$) between control and treated groups. Statistical analysis of tumor data by life-table and contingency table methods revealed no significant ($P > 0.05$) differences among the four groups. Lung tumor findings consisted of adenocarcinomas in two rats of 48 in Group 3 that were killed at 880 days. However, when all CdO-treated groups were pooled and tested by life-table methods for differences in tumor incidences from the controls (Group 1), a statistically significant ($P = 0.043$) increase in mammary tumors was observed. In addition, the frequency of rats with three or more tumors was increased in the high-dose group ($P = 0.044$). Since cadmium has been shown by Chandler et al. (1976) to inhibit testosterone release and increase circulating levels of leuteinizing hormone, a possible tumor promoter, the finding of increased mammary tumors in the males is more than plausible when one considers the rather high background rate normally found in female rats of this strain.

While cadmium, as CdO, did not produce lung tumors under the conditions of this study, the protocol used may not have been as sensitive an indicator of the respiratory carcinogenic potential of cadmium as would a design that included lifetime exposures by inhalation, particularly in reference to the carcinogenicity study by Takenaka et al. (1983) discussed herein. Lung tissue was not analyzed for cadmium content in the Sanders and Mahaffey (1984) study. However, clearance of 80% of an intratracheally instilled dose of 15 ug ^{109}CdO from the lung in male Fischer 344 rats, with an elimination half-life of 4 hours, has been observed (Hadley et al. 1980). In addition, the distribution within the lung of the cadmium was probably not equivalent to that which would have resulted from an inhalation exposure. Oberdoerster et al. (1980) showed, using $CdCl_2$, that after a 1-hour nose-only inhalation exposure, 16% more cadmium was deposited in the alveolar area as compared with intratracheal instillation. Hence, a lifetime inhalation exposure to CdO also might have presented a stronger challenge for carcinogenicity by providing a greater cumulative dose of cadmium within target (lung) tissue.

The increase of mammary tumors observed in the Sanders and Mahaffey (1984) investigation is in keeping with the finding of relatively rapid clearance of CdO from the lungs and translocation into other tissues following inhalation (Hadley et al. 1979) or intratracheal instillation of CdO (Hadley et al. 1980). In view of the positive pulmonary findings with $CdCl_2$ (Takenaka et al. 1983) and less severe but more marked extrapulmonary effects (Sanders and Mahaffey 1984, Hadley et al. 1979) and increased extrapulmonary tissue concentrations (Hadley et al. 1980) with the chemically less soluble CdO, the observation of Hadley et al. (1979) that airborne cadmium may constitute a potential hazard to both lung and extrapulmonary tissues is noteworthy. It is necessary, however, to apply caution when the chemical (rather than the biological or the pulmonary) solubility of cadmium salts is used in predicting the behavior of chemicals in complex biological systems. This view is also supported by the work of Oberdoerster et al. (1979), which showed no difference in the long-term lung clearance rate of inhaled CdO or $CdCl_2$.

Furst et al. (1973), as part of a larger investigation of the induction of mesotheliomas by metal in asbestos, performed a preliminary assessment of the effects of intrathoracic injections of powdered cadmium. The test materials, suspended in saline solution, were injected into the right portion of the thoracic cavity through the intercostal muscles. The authors indicated that injection of 3 mg of cadmium once a month for 5 months did not produce any tumors, but was too toxic. The rats treated with cadmium became emaciated and lethargic. In an effort to reduce the toxicity of the cadmium, a second group of five male and five female Fischer 344 rats were injected intrathoracically with 3 mg of cadmium powder and 6 mg of zinc powder in physiological saline once a month for 5 months. The zinc reduced the overt toxicity of the cadmium. At the end of the 10-month experimental period, 3 of the 10 rats had developed tumors, as compared to 0/20 in the controls. The first of these tumors was evident at 120 days after the first injection. The tumors were diagnosed as mesotheliomas, probably malignant. No tumors were observed in the rats treated with zinc only.

Injection Studies in Mice and Rats

Injection of cadmium metal or certain salts of cadmium has been shown to produce sarcomas at the site of the injection, as well as testicular tumors (Leydig cell, interstitial cell) in experimental animals. These studies are summarized in Table 10. The usefulness of subcutaneous injections in determining carcinogenic potential has been discussed by a number of authors, whose conclusions are summarized below.

Grasso and Goldberg (1966) doubted the usefulness of the technique of assessing the carcinogenic potential of chemicals on the basis of injection site sarcomas. They did indicate, however, that the development of tumors at sites distant from the injection site was very suggestive of carcinogenic potential in the material under investigation. The testicular tumors produced by the injection of cadmium salts certainly fulfill the criteria set forth by these authors for the assessment of positive carcinogenic potential.

Tomatis (1977) reviewed the appropriateness of the subcutaneous injection route for bioassays of carcinogenicity by comparing it with other routes of administration. He surveyed a number of chemicals tested by the subcutaneous injection route in rodents to see if there was a correlation between the capacities of these chemicals to induce local and/or distant tumors in one species and their capacities to induce tumors by another route in another species. A total of 102 chemicals,

TABLE 10. ANIMAL TUMORIGENESIS INDUCED BY CADMIUM INJECTION

Author	Species	Compound	Route	Tumor and incidence
Haddow et al. (1961)	Rats	Ferritin-containing cadmium	s.c.[a]	Sarcomas 8/20 Interstitial cell tumors 10/20
	Mice			Sarcomas 0/20
Heath (1962)	Hooded rats	Cd powder 0.28 g in 0.4 mL fowl serum	i.m.[b]	Sarcomas 2/10 (later in the study 10 more rats developed tumors; the test group they were in was not specified)
		0.014 g in 0.4 mL fowl serum		Sarcomas 3/10
Heath and Daniel (1964)	Hooded rats	Cd powder 0.014 g in 0.4 mL fowl serum 0.028 g in 0.4 mL fowl serum	i.m.	Sarcomas 9/10 Sarcomas 6/8 (2 were killed early)
Kazantzis (1963)	Chester-Beatty rats	25 mg CdS in 0.25 mL physiological saline	s.c.	Sarcomas 6/10
Kazantzis and Hanbury (1966)	Wistar rats	25 mg CdS in 25 mL physiological saline	s.c. i.m.	Sarcomas 6/10, 6/26 Sarcomas 5/14
		25 mg CdO in 0.25 mg physiological saline	s.c.	Sarcomas 8/10
		0.25 mL physiological saline alone		Sarcomas 0/10
Haddow et al. (1964)	Rats	0.5 mg $CdSO_4.H_2O$ in 1.0 ml sterile distilled water once weekly for 10 weeks	s.c.	Sarcomas 14/20; controls 0/15
	Mice	0.05 mg $CdSO_4.H_2O$ in 0.2 mL H_2O once weekly for 11 weeks		0/20 injection site tumors; controls 0/15

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[a] Subcutaneous.
[b] Intramuscular.

(continued on the following page)

TABLE 10. (continued)

Author	Species	Compound	Route	Tumor and incidence
Roe et al. (1964)	Rats	0.5 mg $CdSO_4.H_2O$ in 1.0 mL H_2O once weekly for 10 weeks	s.c.	Interstitial cell tumors 11/15; controls 0/15
		0.05 mg $CdSO_4.4H_2O$ in 0.2 mL H_2O		Interstitial cell tumors 0/16
Gunn et al. (1963)	Albino mice	0.03 mM/kg $CdCl_2$	s.c.	Interstitial cell tumors 20/26; controls 0/25
	Wistar rats	0.03 mM/kg $CdCl_2$	s.c.	Interstitial cell tumors 17/25; controls 0/25
Gunn et al. (1964)	Wistar rats	0.03 mM/kg $CdCl_2$	s.c.	Sarcomas 9/22; controls 0/18 Interstitial cell tumors 21/24; controls 0/18
Gunn et al. (1967)	Wistar rats	1.8 mg $CdCl_2$	simultaneous s.c. and i.m.	Sarcomas 10/23 Sarcomas 3/26
Knorre (1970)	Wistar rats	0.003 mM $CdCl_2$/100 g b.w.	single s.c.	Sarcomas 6/45
Knorre (1971)	Wistar rats	0.003 mM $CdCl_2$/100 g b.w.	single s.c.	Interstitial cell tumors 10/25
Lucis et al. (1972)	Wistar rats	0.02-0.03 mM/kg $CdCl_2$ in isotonic NaCl solution	single s.c.	Interstitial cell tumors 13/15 Sarcomas 2/15 (two animals died early)
Reddy et al. (1973)	Fischer 344 rats	0.03 mM/kg $CdCl_2$	single s.c.	Interstitial cell tumors 16/20; controls 0/10
Furst and Cassetta (1972)	Fischer 344	5 mg Cd powder (suspended in 0.2 mL synthetic trioctanoin)	2 monthly i.m. injections	Sarcomas 26/50
Favino et al. (1968)	Sprague-Dawley rats	1 mg/100 g $CdCl_2$	single s.c.	Interstitial cell tumors 6/6

(continued on the following page)

TABLE 10. (continued)

Author	Species	Compound	Route	Tumor and incidence
Malcolm (1972)	Rats	$CdCl_2$	s.c.	Sarcomas (?) Interstitial cell tumors (?) (Experiment not completed at time of publication)
Levy et al. (1973)	C.B. hooded rats	0.2 mg $3CdSo_4.H_2O$ in 0.2 mL H_2O	weekly s.c. injection into alternate flanks for 2 yrs	Sarcomas 4/25 Interstitial cell tumors 17/25 1 lung adenoma
		0.1 mg $3CdSO_4.8H_2O$ in 0.2 mL H_2O		Sarcomas 1/25 Interstitial cell tumors 17/25 1 malignant lymphoma
		0.05 mg $3CdSO_4.8H_2O$ in 0.2 mL H_2O		Sarcomas 1/25 Interstitial cell tumors 16/25 1 adenocarcinoma of pancreas
		controls - 0.2 mg H_2O only		Sarcomas 0/75 Interstitial cell tumors 48/75 1 squamous carcinoma of tongue 1 benign liver cell tumor
Scott and Aughey (1979)	Rats	0.05 mL injection into 1 mol $CdCl_2$ prostate		Prostate tumors 17/207
	Rats	0.05 mL 1 mol $CdCl_2$	s.c. five times	Negative for prostate
Poirier et al. (1983)	Wistar rats	7.3 mg/kg $CdCl_2$ in 0.9% NaCl	single s.c.	Sarcomas 14/50 Interstitial cell tumors 39/50
		3.6 mg/kg $CdCl_2$ in 0.9% NaCl		Sarcomas 12/50 Interstitial cell tumors 38/50
		controls - 0.9% NaCl		Sarcomas 0/50 Interstitial cell tumors 13/50

which have been reviewed by the International Agency for Research on Cancer (IARC) and have been tested by the subcutaneous injection route as well as by other routes of administration, were surveyed. Of those, 69 were positive for carcinogenic activity when administered by subcutaneous injection and by another route, and 18 were negative or inconclusive whether given by subcutaneous injection or by another route. Nine were positive only when administered by subcutaneous injection, and six were negative by subcutaneous injection and positive by another route. The author concludes that "administration of a chemical by the subcutaneous injection route produced what one could call false negative results for six (5.6%) of the 102 chemicals tested and, if we accept all the criticisms of this route of administration, false positive results for nine (8.7%) of the 102 chemicals tested." Even so, according to the author, it appears that the subcutaneous injection route of administration is not too much worse than any other route of administration.

More recently Theiss (1982) reviewed the IARC data base. He concluded that if a compound produces distant tumors by subcutaneous injection it is almost always tumorigenic by at least one other route of exposure. Theiss recommended that the results of investigations of materials producing tumors at sites other than the injection site should be considered to be as significant as results obtained by routes of administration more relevant to man.

Thus, by all accounts the induction of tumors distant from the injection site is regarded as highly useful in the classification and identification of carcinogens. The recent work of Chellman and Diamond (1984) provides a possible reason for the consistent induction of cancer following injection of cadmium or its salts at other sites. These investigations showed that in the testes, significant amounts of cadmium were not bound to metallothianein, a protein to which cadmium is normally bound, rendering the metal in the tissues less toxic.

Poirier et al. (1983), in addition to observing increased testicular tumors, showed an increase ($P < 0.02$) in pancreatic islet cell tumors following subcutaneous injection over a 2-year period of $CdCl_2$ (22/259, 8.5%) as compared to rats not receiving $CdCl_2$ (3/137, 2.2.%) and surviving more than one year, the time to the first such tumor. In the same report, it was shown that simultaneous injections of magnesium acetate prevented the development of injection-site tumors, but had no effect on testicular tumorigenesis. No inhibitory effect was elicited by calcium acetate in the diet, by simultaneous injection, or by magnesium acetate in the diet.

The induction of pancreatic tumors of $CdCl_2$ is not altogether unexpected since high concentrations of cadmium in the pancreas of humans and animals has been reported (Friberg and Odeblad 1957), and the effects of cadmium on carbohydrate metabolism and insulin secretion are well documented (Ghafghazi and Mennear 1973).

Oral Studies in Mice and Rats

Schroeder et al. (1964 and 1965) conducted two lifetime exposure studies in which Swiss mice were given drinking water containing cadmium acetate at 5 ppm. The purpose of this low exposure level was to simulate the human experience, according to the authors. In the first study, only males experienced decreased longevity in comparison with controls. The mean concentration of cadmium in the kidneys of mice at the end of the study was only 3 ug/g wet weight. This appears to be very low in comparison with the concentrations of 18 ug/g that have been reported in man, and the 13.5 ug/g in rats exposed to 12.5 ug/m^3 reported by Takenaka et al. (1983). The exposed males had fewer "visible" tumors (1/50) than the controls (11/50), a result ($P < 0.005$) which was possibly related to the shortened lifespans of the exposed males. Only abnormal tissues were histopathologically evaluated. The reduced survival times of the animals, and the limited amount of histopathological evaluation that was conducted, limit the usefulness of this study in the evaluation of the carcinogenic potential of cadmium.

In the second lifetime exposure study by Schroeder et al. (1965), male and female Long-Evans rats ingested cadmium acetate at 5 ppm in water as the sole source of fluid; the treated group developed 28/84 tumors versus 24/70 in controls. The authors stated that "no significant differences appeared among the various groups as to type of tumor." This study, like the authors' 1964 study, was complicated by being performed in a low-metal environment and with a diet low in many trace metals. When the essential trace element Cr(III) was added to the diet of one group of rats that were not given cadmium, they thrived better than the control group and had 34/71 tumors (Schroeder et al. 1965).

Malcolm (1972), in one experiment, gave male Chester-Beatty hooded rats up to 0.2 mg of cadmium sulfate subcutaneously and up to 0.8 mg weekly by stomach tube for 2 years. In another experiment, he gave Swiss mice doses of cadmium sulfate in distilled water up to 0.02 mg/5g of body weight subcutaneously at weekly intervals for 2 years. Except for a few sarcomas and Leydig cell tumors seen in the rats given subcutaneous injections (both also seen in the controls), these studies were negative at the time reported.

Experiments with male specified pathogen-free Chester-Beatty hooded rats, using doses of 0.087, 0.18, and 0.35 mg/kg of cadmium sulfate in distilled water given by gastric instillation once weekly for 2 years, were carried out by Levy and Clack (1975). Ninety males received 1 mL distilled water on the same regimen, and served as controls. No difference in tumor incidence between exposed and control groups was observed. It is noted, however, that this particular strain of rats has a very high lifetime incidence of spontaneous interstitial cell tumor formation (75% in the untreated control group), such that "if exposure to cadmium had any effect on the incidence of the lesions it was entirely overshadowed by their spontaneous occurrence," according to the authors. Effects on the prostate were especially scrutinized, with no neoplastic lesions observed. Only a limited number of tissues (kidney, spleen, liver, lung, testes, and prostate) were histopathologically evaluated from 10 rats of the high-dose group and 10 rats of the control group.

Levy et al. (1975) similarly gave groups of 50 male Swiss mice 0.44, 0.88, or 1.75 mg/kg/week cadmium sulfate by gavage for 18 months. A group of 150 male mice served as controls. The stated objective of the study was the detection of an increased incidence of prostate tumors attributable to cadmium, but neither that nor any other treatment-related effect was reported at any of the three dose levels. As in the study with rats, the histopathological examination was not sufficiently thorough to make this constitute a compelling negative study. The set of tissues fixed was limited to prostate, urethra, bladder, stomach, kidney, testes, lung, liver, spleen, seminal vesicles, and coagulatory gland, and these tissues were examined microscopically for only 20 of the high-dose and 20 of the control males, along with any abnormal tissues noted macroscopically. Although measurements of cadmium concentration in various tissues were not made, Levy et al. (1975) speculated that the reason no pathological changes attributable to cadmium were observed during the study may have been that absorption of cadmium through the intestinal tract is low.

An unpublished chronic toxicity study of $CdCl_2$ was conducted at the U.S. Food and Drug Administration (U.S. FDA 1977). The compilation of animals examined pathologically shows that six groups of Charles River COBS (SD) rats, each consisting of 26 to 32 males and 26 to 29 females, were studied. These groups were given 0 (untreated controls), 0.6, 6, 30, 60, or 90 ppm $CdCl_2$ in the diet for 103 weeks. Five males and five females per group were sacrificed at 24 and 52 weeks. All animals were necropsied, and tissues, organs, and tissue masses were examined histopathologically. Kidney tissue from five or fewer males in each sacrificed group was evaluated by electron microscopy; sections of liver and kidney from these animals were stained to assess fibrosis, lipid content, liver glycogen, and the basement membrane of tubuli and Bowman's capsules in kidney.

No significant ($P > 0.05$) differences in survival between control and treated groups were reported, and, excluding interim sacrificed animals, no more than two animals per group died before 77 weeks. Results of necropsy and histopathologic and histochemical evaluations did not show treatment-related effects. Electron microscopy, however, revealed dose-related changes in the form of small cytoplasmic lipid droplets in renal tubular epithelium, increased number of residual bodies in renal nephron cells, and swelling and sloughing of cells in distal tubular epithelium and the collecting ducts of the kidney.

A 2-year oral carcinogenicity study of Wistar rats given $CdCl_2$ was carried out by Loser (1980). Doses of 1, 3, 10, and 50 ppm of cadmium were given in food to 50 male and 50 female rats, with 100 controls of each sex. Food consumption was similar in all the test groups. The mean body weights of treated males were significantly reduced ($P < 0.01$) at the highest dose level. Other than reduced weight in the high-dose males, the male and female treatment and control groups were comparable for weight and mortality. On the basis of a complete histopathological evaluation, the author concluded that there was no significant increase in the incidence of any particular tumor type or in the frequency of tumor-bearing animals.

The reason for the discrepancy between the FDA (1977) study with regard to the lack of effects of cadmium at 60 and 90 ppm as compared to the highly significant effect ($P < 0.01$) at 50 ppm is not readily apparent. Strain differences or differences in dietary factors (such as selenium, zinc, copper, or estrogen concentrations) may account for the lack of comparability.

Summary

Chronic exposure of rats to aerosols of $CdCl_2$ at airborne concentrations of 12.5, 25, and 50 ug/m^3 for 18 months followed by an additional non-exposed 13-month period produced significant increases in lung tumors. An 18-month exposure to 20 ug/m^3 also increased lung tumors among exposed rats. A single 30-minute exposure of rats to CdO did not significantly increase the occurrence of lung tumors in the year that followed. However, increases in mammary tumors and testicular degeneration were observed. The estimated total dose in mg/kg was, however, lower than that producing testicular neoplasia following parenteral administration.

Intratracheal instillation of CdO produced an increase in mammary tumors and an increase in tumors at multiple sites among male rats. Intrathoracic injections of cadmium powder are highly toxic, but when their toxicity is reduced by co-administration of zinc, mesotheliomas develop. Intramuscular or subcutaneous injection of cadmium as metal powder, or as chloride, sulfate, oxide, or sulfide, produces injection-site sarcomas and/or testicular interstitial cell (Leydig cell) tumors after necrosis and regeneration of testicular tissue. A recent study suggests that the incidence of pancreatic islet cell tumors may be increased by administration of $CdCl_2$ by this route. In addition, injection of $CdCl_2$ into the prostate has induced tumors of that tissue. The translocation and long-term pulmonary clearance of cadmium salts do not appear to be related to the chemical's solubility.

Cadmium appears to be much less potent as a carcinogen by ingestion than by injection or inhalation, regardless of the site of cancer induction. For example, the total dose of inhaled cadmium in the Takenaka et al. (1983) study, where the rats developed a 71% incidence of lung cancer, was about 7 mg (0.25 m^3/day x 0.05 mg/m^3 x 365 days/year x 1.5 years). By contrast, in the Schroeder et al. (1965) drinking water study in rats, which had one of the smallest total doses of all of the ingestion studies, a total dose of about 60 mg (5 ppm x 0.5 x 0.35 kg x 730 days) induced no cancer responses. If a 10% upper limit of detection of tumors in the Schroeder et al. (1965) study is assumed, the highest reasonable potency for cadmium via ingestion is about 0.0017 (0.1/60), compared with a potency of about 0.1 (0.7/7) for inhalation. While it is possible that cadmium is not at all carcinogenic by ingestion because of very limited absorption, the negative animal evidence can only set an upper limit on the carcinogenic potency of ingested cadmium, which in the rat appears to be about two orders of magnitude less than for inhalation.

In 1982 the IARC concluded that sufficient evidence existed for the determination that cadmium is carcinogenic in animals. The IARC was aware at that time of the negative findings of Loser (1980) following dietary administration of $CdCl_2$ to laboratory animals. However, studies reporting a marked carcinogenic response in rats to inhalation of $CdCl_2$ aerosols were not available to the IARC for consideration, nor were the highly suggestive reports of pancreatic islet tumors following parenteral administration of $CdCl_2$ (Poirier et al. 1983), and of male mammary tumors following intratracheal instillation of CdO (Sanders and Mahaffey 1984). Apparently the IARC did not consider the intratracheal induction of mesotheliomas reported by Furst et al. (1973) or the induction of prostate tumors by injection of $CdCl_2$ into that tissue (Scott and Aughey 1979). As a result of these newer investigations, together with additional information suggesting a distribution not based on chemical solubility, the carcinogenic risks of cadmium and its compounds are now seen to be greater than originally anticipated.

EPIDEMIOLOGIC STUDIES

The epidemiologic studies reviewed here deal specifically with cancer risks resulting from cadmium exposure. Although five of these studies were reviewed in the OHEA Health Assessment Document for Cadmium (U.S. EPA 1981), they are covered here also for the convenience of the reader.

Potts (1965)

Potts (1965) reported the results of a clinical study of an unstated number of current and former employees of a British alkaline battery factory who were exposed to cadmium oxide dust beginning in 1920 and ending in 1963. In 1946 the manufacture of these batteries was moved to a new location not far from the site of the earlier factory. The first measurements of cadmium dust in the air were made in 1949. At that time, the cadmium content of the air varied from 0.6 to 2.8 mg/m^3 in the platemaking and assembly shops to 236 mg/m^3 in the negative active material department. After the installation of local exhaust ventilation in 1950, cadmium in the air was reduced to less than 0.5 mg/m^3. Improvements to the exhaust system in 1956 further reduced the cadmium dust to less than 0.1 mg/m^3. The policy at the time of the study's publication was to take steps to reduce exposures whenever the measurement of cadmium dust exceeded 0.5 mg/m^3.

Of 70 battery workers for which Potts's clinic had medical records and who were exposed for at least 10 years, proteinuria was observed in 44%. Although no comparison group was provided, this number is probably excessive, since proteinuria is the result of renal tubular dysfunction. A 200-248 ug/day cadmium dietary intake over a 50-year exposure period is required to produce the critical renal cortex concentration associated with renal dysfunction. Only 1% of Americans ingest more than 50 ug/day (U.S. EPA 1981). However, the author did note that earlier studies of the urine protein of cadmium-exposed workers in this same plant had revealed "similar characteristics" to those of the present study. Four individuals with persistent proteinuria were examined further. Two of them ultimately died. Kidney function tests prior to death revealed no abnormalities, nor were any gross abnormalities observed following microscopic examination of the kidneys of the deceased.

In a second phase of this study, Potts claimed that a "careful search" produced records for a total of 74 men who had been exposed to cadmium dust for more than 10 years. Eight of these men had died. The author did not reveal whether the source of this information was his clinic's medical records or the employment records of the factory, nor did he specify the relationship between these 74 men and the 70 battery workers mentioned earlier. Furthermore, the source of his information on the eight deceased individuals was not given, although presumably it came from his clinical files. Five of the eight deaths were reportedly due to cancer; three of these were cancer of the prostate. The death data from Potts's paper is summarized in Table 11. Whether or not the author made any attempt to determine the vital status of the remaining 66 individuals is unclear. Since all of the deaths occurred in the early 1960s, and nearly all of these individuals had had lengthy exposures, it can be inferred that they had all been exposed to the highest cadmium dust levels that existed at the plant during their years of employment prior to 1950. No information was given on workers exposed for fewer than 10 years.

In the absence of selection bias (a distinct possibility if clinical records were used), the distribution of the eight deaths is striking, as was noted by the author. But because of the possibility of selection bias, the lack of a comparison group, and the unknown ages of the 74 members of this population, it is impossible to determine whether the observation of three prostate cancer deaths is statistically significant. Therefore, this study provides only the suggestion of an association of prostate cancer and exposure to cadmium.

TABLE 11. MORTALITY DATA FOR CADMIUM WORKERS EXPOSED FOR MORE THAN 10 YEARS (Potts 1965)

Year of death	Age	Length of cadmium exposure (yrs)	Cause of death
1960	65	31	Auricular fibrillation
1960	75	14	Carcinoma of prostate
1961	65	37	Carcinoma of prostate
1962	63	34	Bronchitis and atheroma
1962	78	18	Bronchitis
1963	53	35	Carcinoma of bronchus
1964	65	38	Carcinoma of prostate
1964	59	24	Carcinomatosis

Kipling and Waterhouse (1967)

Kipling and Waterhouse (1967), in a letter to The Lancet, reported on 246 workers who had been exposed for a minimum of one year to cadmium oxide dust. The authors compared the number of cancers observed from several sites with the number expected from those sites based on incidence rates from the Birmingham Regional Cancer Registry. The number of observed cancer deaths of the prostate was significantly greater than expected (4 observed vs. 0.58 expected, $P < 0.003$). Three of the four prostate cancer cases are the same as those reported in Potts's paper (personal communication from Kipling to the IARC in 1976), indicating that some overlapping is acknowledged, and therefore the two studies cannot be said to be independent of each other. No significant differences between observed and expected deaths were found for cancer of the bronchus, bladder, testis, or for cancers of all sites.

Latency period, although obliquely referred to in the letter, is poorly addressed. Furthermore, the letter states that expected cases were calculated by "computing the number of cases of cancer which would be expected to occur in such a group of men of known age" and by excluding the time spent in other jobs or retirement. It is not clear how the latter was to be done; the discussion is sketchy at best. The authors mention that "judging from work in similar fields, fairly short exposure may be sufficient to initiate a tumor." Whether this generalized conclusion can be extended to the specific case of cadmium exposure and cancer remains uncertain. The authors' failure to allow for a sufficient latency period weakens the significance of their findings. Because of these problems and the lack of an adequate discussion of the derivation of expected deaths, the results, although statistically significant, cannot be considered definitive with respect to the carcinogenicity of cadmium.

Humperdinck (1968)

Humperdinck (1968) reported on mortality among 536 people who worked or had worked at an alkaline dry cell battery plant during the period 1949-67 and who had been exposed to cadmium hydroxide and "to a large extent nickel hydroxide." Seventeen of the 536 had died, five from cancer. Of the five who died from cancer, two died from lung cancer, one from liver cancer, one from prostate cancer, and one from cardiac cancer. The length of exposure to cadmium for these cases was: lung, 2.3 years and 9.3 years; liver, 3.5 years; prostate, 6.4 years; and cardiac, 3.0 years.

There was no comparison group for the 1949-67 time period. However, the author did compare the average of the cancer death rates for the years 1963-66 in the city where the plant is located with the average 1963-66 rate for the whole plant and the average 1963-66 rate for the departments of the plant where there was exposure to cadmium hydroxide. The author did not state whether these rates were age-adjusted, race-adjusted, or sex-adjusted. No differences were found among the three rates or in the proportion of lung cancer deaths between the city population and the plant population. The proportion of lung cancer deaths for the department where cadmium exposure occurred was not reported.

Previously, Baader (1951) had reported on "20 to 30 males and females" suffering from chronic cadmium poisoning at the same dry cell plant. Of this group, Humperdinck reported that four of eight had died, one of lung cancer; these four are included in the seventeen deaths described previously. No mention is made of any of the other "20 or 30" workers.

Because Humperdinck found no excess cancer mortality among workers exposed to cadmium when compared to the city population or to the plant population as a whole, he concluded that there was insufficient information to establish an association between cadmium and cancer.

A major weakness of this study is that it did not include an appropriate comparison group for the years of the study, 1949-67. Comparison of average death rates for the years 1963-66 among the city, plant, and cadmium departments is not appropriate since it is not known whether all workers in the cadmium departments for the years 1963-66 had experienced a latency period of sufficient duration to have developed cancer. Secondly, there is no indication that the city population or the population of the rest of the battery plant were similar enough to the cadmium-exposed group in terms of race, sex, smoking habits, age, etc. to make these groups objectively comparable. Third, had a proper comparison group been used and an increase in cancer among workers exposed to cadmium been demonstrated, a possible confounding variable would have been the concomitant nickel exposure to which these workers were subjected, since nickel has previously been associated with cancer of the lung, nasal sinus, large intestine, mouth, and pharynx (Fraumeni 1975).

In conclusion, the study design and methods of Humperdinck render his data inadequate for the assessment of an association between cadmium exposure and cancer.

Holden (1969)

Holden (1969), in a letter to The Lancet, reported on 42 men exposed to cadmium fumes from 2 to 40 years. He stated that six of the men had been exposed to concentrations of cadmium in excess of 4 mg/m^3, and the remainder had been exposed to an average concentration of 0.1 mg/m^3. The author reported that of the 42 men, one developed a carcinoma of the prostate and one developed a carcinoma of the bronchus.

No evaluation of the cancer risk from cadmium can be made on the basis of this letter, since the author did not report important variables such as age, time since first exposure, and smoking history.

Kolonel (1976)

Kolonel (1976) compared the cadmium exposure of 64 cases of renal cancer to 197 nonmalignant digestive disease controls and 72 colon cancer controls. According to the author, "a cancer control group was included to address the problem of potential noncomparability" between cases and controls when a non-cancer control group was used. Cases and controls were taken from patients admitted from 1957 to 1964 to Roswell Park Memorial Institute, Buffalo, New York. Cadmium exposure was assessed using data on occupational exposure, cigarette smoking, and dietary intake. A person was considered to have experienced occupational exposure to cadmium only if he had worked for one or more years at a high-risk job in a high-risk industry. High-risk industries included electroplating, alloy-making, welding, and the manufacture of storage batteries. A person was considered to be exposed to cadmium through smoking if he had at least 10 "pack-years" of cigarette use during a lifetime. Dietary exposure to cadmium was determined by applying reports of cadmium content in foods to individual dietary histories based on a frequency recall for a one-week period. An individual was considered exposed through diet if his mean daily intake exceeded the third quartile, determined from the distribution of intakes for the noncancer control group.

The author found that the odds* of developing renal cancer in occupationally-exposed patients who smoked were 4.4 when compared to controls who also smoked and had nonmalignant diseases of the digestive system. This is significant at $P < 0.05$. The odds of developing renal cancer in patients who were occupationally exposed were 2.5 ($P < 0.05$) when compared to colon cancer controls. The latter is not significant ($0.05 < P < 0.10$). Because of the finding of a greatly increased risk† when the effects from smoking and occupational exposure were added together, the author concluded that the effects of smoking and occupational exposure must be synergistic.

The odds of developing renal cancer when consideration is given to cadmium exposure through cigarette smoking only, and separately through diet only (utilizing colon cancer controls), were 1.2 and 1.6, respectively, neither of which was significant ($0.05 < P < 0.10$, two-tailed).

A major criticism of this study is the confounding exposures to other industrial materials in the electroplating, alloy-making, welding, and storage battery manufacturing industries. The author stated that renal cancer resulting from cadmium exposure is biologically plausible because the kidney concentrates cadmium to a greater degree than any other organ. Furthermore, Kolonel pointed out, on the basis of an earlier study by Ellman (1959), that the kidney contains the body's highest concentration of sulfhydryl groups, which are often found in zinc-containing enzymes. Cadmium inhibition of a variety of sulfhydryl-containing enzymes has been reported, the author notes, and this may be the mechanism of action. The kidney concentrates many trace metals, however, and a variety of metals are found in the industries mentioned above, including nickel, lead, and zinc. Also, it is interesting to note that the odds ratio for occupational exposure to cadmium is significant ($P < 0.05$) only when compared to noncancer controls, but not significant ($0.5 < P < 0.10$) when compared to colon cancer controls. This indicates that the renal cancer cases may not be comparable to the noncancer cases, and selection bias may have occurred.

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*Although the author referred to "relative risk" in his article, it is more correct to use the term "odds ratio" or "estimated relative risk."

†Risk in this context is an estimated relative risk derived by use of the odds ratio.

Smoking has previously been associated with kidney cancer (Wynder et al. 1974, Schmauz and Cole 1974, Kahn 1966, Hirayama 1977) as well as with cancers of other sites. Although cadmium may be the carcinogen in tobacco smoke that causes kidney cancer, the issue is confounded by the presence in tobacco smoke of many other carcinogens as well. Although the smoke may serve only as a possible synergist or a carrier mechanism for cadmium exposure from other sources, it remains to be demonstrated that cadmium is the agent of concern in smoking.

In conclusion, Kolonel's study provides suggestive, but not sufficient evidence that cadmium is a renal carcinogen. More studies, epidemiologic and animal, are necessary to adequately address the issue.

Lemen et al. (1976)

Lemen et al. (1976) conducted a historic prospective study on 292 white male employees of a cadmium smelter who had worked a minimum of 2 years in the smelter at some time during the period from January 1, 1940 to December 31, 1969.

Vital status was determined for this group through January 1, 1974. Death certificates listing the causes of death were acquired for 89 of a reported 92 deceased. Some 20 (6.8%) remained lost to follow-up. For comparison, expected deaths by cause were generated through a modified life-table technique based on person-years multiplied by the corresponding age, calendar time, and cause-specific mortality rates for the total United States white male population.

The authors stated that the smelter was engaged in the production of cadmium metal and cadmium compounds. However, they reported that some lead was also produced. The plant ceased full-scale lead production in 1918 and began to produce arsenic instead. In 1925, arsenic production ceased and cadmium production began. The authors cited an industrial hygiene survey in 1947 that had reported average air concentrations of cadmium fumes ranging from 0.04 to 6.59 mg/m^3 and cadmium dust at 17.23 mg/m^3, but it was reported in that survey that most operations in the plant had cadmium air concentrations of lower than 1.5 mg/m^3. The present study included a 1973 industrial hygiene evaluation of cadmium dust levels which stated that 8-hour time-weighted average (TWA) gross concentrations of cadmium ranged infrequently up to 24 mg/m^3, but generally remained below 1 mg/m^3. The authors reported, following a 1973 industrial hygiene survey, that a respirator program had been instituted at the plant, which had allegedly reduced exposure by a factor of 10, although the workers tended to remove the respirators because of their inconvenience. Two air measurements taken in the preweld department showed that in addition to air concentrations of 74.8 and 90.3 ug/m^3 of cadmium, arsenic was measured at 0.3 and 1.1 ug/m^3. This is about 1% of the cadmium measurement. In the retort department, however, where the cadmium concentration was measured at 1,105 ug/m^3, arsenic measured 1.4 ug/m^3, which was about 1/1,000 that of cadmium. On the other hand, analyses of bulk samples revealed 42.2% to 70% cadmium, 3.53% to 6% zinc, 0% to 4.3% lead, and

0.02% to 0.3% arsenic. The remaining ingredients were not identified. The authors concluded that the exposures from the remaining ingredients were insignificant.

A statistically significant excess of total malignant neoplasms (27 observed vs. 17.6 expected, $P < 0.05$) was found, as well as a statistically significant excess of malignant respiratory disease (12 observed vs. 5.1 expected, $P < 0.05$). Without regard to latent effects, an excess of prostate cancer was reported by the authors to be not significant (4 observed vs. 1.15 expected). However, utilizing a one-tailed Poisson variable, the Carcinogen Assessment Group (CAG) found the latter observation to be statistically significant ($P < 0.05$). After a lapse of 20 years from initial exposure, the finding of a statistically significant excess in prostate cancer (4 observed vs. 0.88 expected, $P < 0.01$) was even stronger.

Information concerning exposure and latency of the four prostate cancer cases is given in Table 12.

TABLE 12. PROSTATE CANCER DEATHS AMONG CADMIUM SMELTER WORKERS WITH MORE THAN 2 YEARS EXPOSURE
(Lemen et al. 1976)

Case	Age	Exposure	Latency	Date of death
1	71	4	32	2/26/72
2	77	13	25	3/19/68
3	79	18	31	12/10/60
4	64	17	26	4/03/51

Of the 12 malignant respiratory cancer cases, the cell types of eight were known. Three were squamous cell carcinomas, one was an undifferentiated small cell carcinoma, three were anaplastic carcinomas, and one was an oat cell carcinoma. Unfortunately, smoking histories were not available for members of the cohort. Therefore, confounding of the results due to smoking could not be assessed. Furthermore, Lemen et al. reported the presence in the smelter of other substances, including arsenic, lead, and zinc, that are either known or suspected carcinogens. Any conclusions made from this study regarding the carcinogenic potential of cadmium should be tempered with the knowledge that these other substances were also known to be present in the atmosphere of the smelter. In addition, it is apparent that the authors did not identify all of the constituents of the processed ores, since the percentages given do not add up to 100%.

However, when consideration is given to the fact that the vital status of 6.8% of the study cohort remains unknown, it is apparent that additional causes of death in this group of 20 people potentially might have added additional prostate cancers to the observed deaths. In contrast, the expected deaths were overestimated because person-years were counted to the cut-off date for these same individuals. This could slightly bias downward the finding of an excess risk of prostate cancer and bronchogenic cancer.

This study provides support to the supposition that exposure to cadmium is associated with a significant excess risk of prostate cancer. The other metals known to be present have not been shown to be associated with an elevated risk of prostate cancer. On the other hand, the presence of arsenic in the atmosphere of the smelter, and the possibility of increased smoking among these workers, might be confounding factors that reduce the significance of the association between bronchogenic cancer and cadmium exposure in the workers.

McMichael et al. (1976a, b)

McMichael et al. (1976a), as part of a historic prospective study of cancer mortality among rubber workers, followed 18,903 active and retired male workers, aged 40 to 84, for a period of 10 years. They were divided into four separate cohorts, each consisting of workers from the four tire manufacturing plants of the companies under study.

The mortality experience during the 10-year observation period was determined from death claims filed with the companies under the group life insurance policy in effect. In three of the four plants, workers were included if they were employed on January 1, 1964, whereas in the fourth plant they were included if they were employed on January 1, 1963. About 1% were lost to follow-up, and death certificates listing causes of death were obtained for 98% of the deceased. Expected deaths were calculated based on the 1968 U.S. male race- and age-specific death rates. The calculation of standard mortality ratios (SMRs) utilizing such rates produces an underestimate of the risk. This bias, known as the "healthy worker effect," is a consequence of the selection of the healthiest individuals into a given workforce from the general population from which the expected deaths were derived. Apparently, little turnover occurred in these four plants because the former employees who switched to another place of employment formed the group of 1% lost to follow-up during the 10-year follow-up period.

The total number of deaths equaled 5,160, for an overall SMR of 94. The total number of cancer deaths equaled 1,014 for an SMR of 100, while that for prostate cancer was 119 (103 observed, nonsignificant at $0.05 < P < 0.1$). The authors hypothesized an association of prostate cancer with the compounding and mixing areas of the four plants, work areas that entail contact with metallic oxides (including cadmium oxides). The authors also hypothesized an association of prostate cancer with three additional work areas (cement mixing, janitoring, and trucking) of one particular plant after "exploratory work-history" analyses were completed for stomach, bladder, and prostate cancer, lymphosarcoma, and Hodgkin's disease at this plant.

In a similar mortality study of just one of the above four plants, McMichael et al. (1976b) confirmed a significant excess risk of prostate cancer (SMR = 140, observed = 53, $P < 0.05$) in 6,678 male rubber workers, and found that the risk was associated with the calendering, janitoring-trucking, compounding, and mixing occupational groups. He stated that cadmium compounds were used as vulcanization (curing) accelerators in these broad occupational groups. The method of classifying workers utilized by McMichael et al. is discussed further in a later critique by Goldsmith et al. (1980).

The object of the earlier McMichael et al. (1976a) study was not to single out the association of prostate cancer with cadmium exposure as the main topic of study, but rather to examine site-specific cancer mortality, in general, in rubber workers. Hence, the authors found excesses in cancer mortality at a number of different sites, but did not test the significance of any of these excesses. Data from the McMichael et al. (1976a) study are summarized in Table 13. The tests of significance were calculated by the CAG using the method of Chiang (1961).

One major problem with this study is that rubber workers are potentially exposed to numerous organic and inorganic chemicals, some of them known or suspected carcinogens, including benzene, which is a known human carcinogen. The SMRs may thus be confounded by additional exposures to chemicals other than cadmium. Exposure levels for the many different compounds found in these plants are not given.

A second problem with this study is the relatively short observation time (10 years) from the beginning of the study to its cut-off date. This is an insufficient period in which to assess latent effects, and in fact, no data are presented in which latency is considered. This cohort should be followed for several additional years before a final conclusion is made regarding carcinogenic effects resulting from exposure to cadmium. While the paper is of interest as a basis for further studies, it does not provide adequate evidence for the association of cadmium with prostate cancer.

TABLE 13. STANDARD MORTALITY RATIOS (SMRs) BY SITE
(McMichael et al. 1976a)

Site	Observed deaths	SMRs	Probability of occurrence[a]
Lymphatic leukemia	20	158	0.039
Stomach	80	148	<0.001
All leukemias	46	130	0.073
Hodgkin's disease	32	129	0.150
Prostate	103	119	0.077
Colon	103	116	0.131
Pancreas	57	103	0.826
Bladder	32	92	0.638
Respiratory	252	85	0.002
Rectum	27	82	0.303
Brain, central nervous system	14	78	0.352
All cancer	1014	100	1.000
All causes	5106	94	<0.001

[a] Taken from Chiang (1961).

Monson and Fine (1978)

In another mortality and morbidity study of cancer in 13,570 white male rubber workers (Monson and Fine 1978), an elevated risk of prostate cancer was noted (4 observed, 0.04 expected, $P < 0.05$) in two unrelated departments, material conservation and final finish. In no other department of this plant was an elevated risk of prostate cancer evident. However, the authors do not attribute this excess risk to any common exposure in these departments, except possibly to oils used in machine maintenance. The authors claim that cadmium exposure was not "appreciable" in this plant. Data on the U.S. white male population provided the comparison population for the expected prostate cancer deaths. This study, which uses the same plant that was studied earlier by McMichael et al. (1976a, b) and later by Goldsmith et al. (1980), does not support the hypothesis suggested by McMichael et al. that cadmium in the plant was responsible for the excess risk of prostate cancer.

Kjellstrom et al. (1979)

Kjellstrom et al. (1979) reported on a historic prospective cohort study of 269 male Swedish cadmium-nickel battery factory workers and 94 Swedish male cadmium-copper alloy factory workers having more than 5 years exposure since the factories began production. As an internal reference group, the study also included 328 alloy factory workers who had been employed in the alloy factory for at least 5 years but had not been exposed to cadmium. It was estimated that the average cadmium levels for one of the two factories were as follows: in excess of 1 mg/m^3 prior to 1947, 200 ug/m^3 between 1962 and 1974, 50 ug/m^3 in 1974, and below 5 ug/m^3 at the time of the study. At the other factory, concentrations were in the range of 100 to 400 ug/m^3 in the mid-1960s and 50 ug/m^3 in 1971 and after. The battery study population was also exposed to nickel hydroxide dust.

National average age- and cause-specific death rates and cancer incidence rates were used to generate expected deaths and expected new cancer cases in the two study groups. New cases of cancer were found in the battery factory by matching the names of the 269 workers with those of the Swedish National Cancer Register. This was not done with the alloy factory workers. With respect to mortality in the battery factory, 43 deaths occurred between 1949 and 1975, of which 8 were due to cancer. This contrasts with 67 expected total deaths during the same period. No further breakdown is given of the cancer deaths, and no expected cancer mortality is given. However, the authors state that there was no increase in "general" cancer mortality. Furthermore, the total number of new cases of cancer equaled 15 during the period from 1959 to 1975, while the expected number of new cases equaled 16.4, based on incidence data provided by the Swedish National Cancer Register. A breakdown by site is given in Table 14. Only cancer of the nasopharynx was found to be significantly in excess (2 observed vs. 0.2 expected, $P < 0.05$) possibly due to exposure to nickel dust.

In the alloy factory, only "preliminary" calculations of prostate cancer mortality were done; cause-specific mortality and incidence were not examined in these workers. Among 94 exposed workers, four prostate cancer deaths were noted versus 2.69 expected ($P = 0.29$). In the reference group of 328 unexposed workers, four prostate cancer deaths were noted versus 6.42 expected ($P = 0.23$) (Table 15). A corrected "healthy worker effect" risk ratio was derived by dividing the risk of developing prostate cancer in the exposed group by that of the reference group. The resulting ratio was 2.4 ($P = 0.087$), which is still nonsignificant.

Although the results of these two studies are not significant with respect to prostate cancer, and basically inconclusive because of the small study groups, they do suggest a positive association of prostate cancer and exposure to cadmium.

TABLE 14. EXPECTED AND OBSERVED NEW CASES OF CANCER BETWEEN 1959 AND 1975 IN THE WHOLE GROUP OF BATTERY FACTORY WORKERS (N = 228)

(Kjellstrom et al. 1979)

Site	Cancer cases Expected[a]	Observed	Risk ratios
Prostate	1.2	2	1.67
Lung	1.35	2	1.48
Kidney	0.87	0	0
Bladder	1.07	1	0.93
Colon-rectum	2.25	5	2.22
Pancreas	0.60	0	0
Nasopharynx	0.20	2	10.0[b]
Other	9.81	3	0.31
All sites	16.4	15	0.91

[a] Expected deaths based on Swedish National Cancer Registry.
[b] Statistically significantly greater than 1 ($P < 0.05$).

TABLE 15. CUMULATIVE EXPECTED AND OBSERVED NUMBER OF PROSTATIC CANCER DEATHS FROM 1940 TO 1975 AMONG ALLOY FACTORY WORKERS

(Kjellstrom et al. 1979)

	Prostatic cancer deaths Expected	Observed	Risk ratios	P value
Exposed group	2.69	4	1.49	0.29
Reference group (N = 328)	6.42	4	0.62	0.23

Two problems with this work are apparent. The first is that terminated employees were apparently not included in any of the study cohorts unless they had died. The resulting cohorts are healthier than the general population because former employees, who would be expected to carry the greatest burden of potential disease, are not represented. These employees are represented in the general population's death rates, however. The net result is to overestimate the expected deaths, thus masking the potential risks to battery workers.

The second problem is that, because the Swedish National Cancer Register was not established until 1959, the study's incidence data would not have included cancer cases occurring in the 1950s, thus leading to an underestimation of new cancer cases.

Another potential source of selection bias would be the exclusion of all members with incomplete information in the factory files. However, since there is no reason to assume differential selection of subjects for study through this procedure, it may not be a problem.

Goldsmith et al. (1980)

In a later case-control study by Goldsmith et al. (1980) of prostate cancer in one of the four tire and rubber manufacturing plants studied earlier by McMichael et al. (1976a, b), an excess risk of prostate cancer could not be directly attributable to cadmium because no evidence could be found that cadmium was used regularly in the study plant. The authors identified some 88 cases of prostate cancer from death certificates in the years 1964 to 1975. These were matched with 258 controls on the factors of age, race, and date of entry into the plant. Only the batch-preparation work area produced a statistically significant risk ratio ($P < 0.025$) over the exposure periods of (1) more than a month, (2) more than 24 months, and (3) more than 60 months. No identifiable use of cadmium was noted by the authors in this work area. The methods employed in this study, i.e., the technique of grouping employees according to general production areas called occupational title groups (OTGs) for analysis of work history data, tend to result in distorted risk estimates of the carcinogenic potential of substances to which individuals might be exposed in the workplace. In any given OTG, employees who may never have been exposed to any potential carcinogen are lumped together with employees who were exposed to one or more substances, some of which might be classified as potential carcinogens. It becomes difficult to attribute a significant risk ratio to any particular substance in question under these circumstances. Furthermore, since this was a study of only one of the four original plants, the possibility remains that cadmium might have been used in the remaining three plants. Further investigatory work must be done to identify any and all uses of cadmium in the three remaining study plants. It might have been more appropriate to conduct case-control studies of prostate cancer in all four study plants. Instead of using "assignment to particular OTGs" as an indicator of excess risk, it would have been more appropriate to use direct evidence of exposure to cadmium as the dependent variable of interest. Similarly, a case-control study of lung cancer and risk of exposure to cadmium might also be initiated in the rubber industry.

This study does not support the earlier McMichael hypothesis that the excess risk of prostate cancer might have been due to exposure to cadmium compounds used as vulcanization accelerators. Some questions remain, however, about the choice of the study population and the use of OTGs in assessing exposure.

Holden (1980)

Holden (1980) reported the results of a preliminary cohort mortality study of workers in a British cadmium factory who were employed at some time between August 1940 and August 1962, and were followed until December 31, 1979. Iron and brass foundry workers in a second factory served as controls. The cadmium factory data were subdivided by the author into two parts for purposes of analysis. One section of the building contained the cadmium-copper alloy department, where 347 men worked for a minimum of 12 months. Another 624 men worked for a minimum of 12 months in the remaining part of the factory. The latter group was dubbed "vicinity" workers by the author because they worked in the building but not in the cadmium-copper alloy department. Another 537 brass and iron workers were employed in the second British factory for a minimum of 12 months, and their social and physical environments were reported by the author to be similar to those of workers in the first factory.

Industrial hygiene surveys carried out at the cadmium factory in 1953 and 1957 showed the mean level of airborne cadmium in the cadmium-copper alloy department to be 70 ug/m^3 (S.D. = 62 ug/m^3), based on 12-hour sampling, while the mean level in the other parts of the building (the "vicinity") was 6 ug/m^3 (S.D. = 8 ug/m^3). The author reports that vicinity workers were exposed to considerably less cadmium than were the cadmium-copper alloy workers. Follow-up was over 95% complete on all three subcohorts. Expected deaths were generated on the basis of death rates for England and Wales in 5-year age intervals.

A statistically significant elevated risk of dying from all causes (observed = 158, SMR = 112) was evident in the cadmium-copper alloy workers. This excess was not due to malignant neoplasms. The excess risk remained when malignant neoplasms were excluded (observed = 122, SMR = 113). Mortality from neoplasms was not significant in the cadmium-copper alloy workers, except for leukemia (observed = 3, SMR = 441, $P < 0.05$). The author contends that the excess risk observed overall in the study was due to deaths from pulmonary disease. On the other hand, a statistically significant elevated risk of cancer in general (observed = 72, SMR = 120) was apparent in vicinity workers, due chiefly to significant excesses of cancer in two sites: the lung (observed = 36, SMR = 138,

$P < 0.05$) and the prostate (observed = 8, SMR = 267, $P < 0.01$). The author attributed the elevated risk of lung cancer in these workers to the presence of metals other than cadmium, including arsenic. The vicinity workers were reported by the author to have been involved in the manufacture of arsenical copper, and during its refining, to have been exposed to silver and nickel. However, no environmental measurements are reported to have been taken of any of these other metals anywhere in the building in which both groups worked. It was reported by the author that a "considerable evolution of cadmium oxide fumes" resulted when cadmium was dumped into the much hotter molten copper to form cadmium-copper alloy. This effect resulted because cadmium boils at a much lower temperature than that of copper.

With respect to prostate cancer, the author noted the absence of a dose-effect relationship since five of the eight prostate cancers occurred to individuals who were exposed for less than 15 years. Of these five, three were exposed for only one year, if it is assumed that "years of exposure" means years of employment throughout the entire plant. The author attributes only three of the prostate cancer deaths to cadmium exposure because the remaining five were exposed for a "relatively short time." This last observation is somewhat strong in view of the fact that every prostate cancer death occurred 15 or more years following initial exposure. Latency as a factor was not considered in calculating expected deaths, so that the actual risk of prostate cancer may have been greater in vicinity workers. With respect to the risk of prostate cancer in the cadmium-copper alloy cohort (observed = 1, SMR = 63), the numbers involved are too small to warrant the author's finding of no excess risk. In addition, if both the cadmium-copper subcohort and the vicinity workers are re-evaluated only after more than 15 years of follow-up, the chances of detecting a significant prostate cancer risk in the cadmium-copper workers is probably nonexistent, while at the same time, a better estimate of the risk of lung cancer attributable to cadmium exposure in both subcohorts might be had.

It should be noted that the work force of any factory may be rotated many times during the factory's operating life. The fact that cadmium-copper alloy workers, under the author's definition, apparently experienced a lower risk of prostate cancer than did "vicinity" workers may not be unexpected, since it is possible that many of the eight cases may have worked in the cadmium-copper alloy department as well as in the remaining part of the plant at some time during their working careers.

The observed risk of cancer may actually be greater than calculated because of the presence of the "healthy worker" effect, in which less than expected mortality is seen in the control group not only in the overall risk of death from all causes (observed = 95, SMR = 88), but also with respect to the risk of cancer (observed = 21, SMR = 83). If latency had been considered in this study, this confounding effect could have been eliminated.

Because of the preliminary nature of the findings of excess lung and prostate cancer in "vicinity" workers, and further questions that need to be answered regarding the extent of exposures to cadmium, the findings of an excess risk of prostate cancer in these workers should be regarded only as suggestive. The finding of an excess risk of lung cancer due to cadmium exposure must also be considered only suggestive at this time because of the possible confounding effects of smoking and of exposure to other metals such as arsenic, and because of the lack of a dose-response relationship.

Sorahan (1981)

Sorahan (1981), in a preliminary report to the Third International Cadmium Conference, related the findings of a historic prospective mortality study of 3,026 nickel-cadmium battery workers employed prior to and during the period from 1946 to June 30, 1980, who had worked at least one month. A subset of these same workers had been studied earlier by Kipling and Waterhouse (1967). The Sorahan (1981) cohort was derived from workers who had been employed in two separate factories, which were amalgamated in 1947. The earliest mention of cadmium in the air breathed by these workers was reported in 1949. In the platemaking assembly shops, the cadmium content in the air ranged from 0.6 to 2.8 mg/m^3, but in the "negative active material" department, where cadmium oxide powder was prepared, the levels were reported to be "considerably higher," although no numbers were provided. Extensive local exhaust ventilation was installed in 1950, and as a consequence, cadmium levels in the air were reduced to below 0.5 mg/m^3 in most parts of the factory. By 1967, when a new platemaking department was built, the level of cadmium oxide dust in the air had been reduced to less than the threshold limit value (TLV) of 0.2 mg/m^3. From 1975 to the end of the study, the factory's levels of cadmium oxide dust were within the current TLV of 0.05 mg/m^3.

For the purposes of analysis, the author divided his cohort into 566 female employees, 1,066 male employees who were first employed before the amalgamation in 1947, and 1,494 males who were first employed after the amalgamation.

Standard mortality ratios (SMRs) were computed. Expected deaths were generated on the assumption that the general population rates for England and Wales were operant in the study cohorts. Overall, the observed number of male deaths from all causes was slightly less than expected (observed = 591, SMR = 97). With respect to all forms of cancer, there was virtually no difference between observed and expected deaths (observed = 152, SMR = 100). On the other hand, a deficit of cancer deaths occurred to the subcohort of male employees who had been employed prior to the amalgamation (observed = 80, SMR = 84). But in males who were employed for the first time after the amalgamation, a significantly increased risk of total cancer deaths was apparent (observed = 72, SMR = 129, $P < 0.05$). This increased risk was partially attributable to an excess of lung cancer (observed = 32, SMR = 134, $0.05 < P < 0.10$) in the latter subcohort. In females, a slight nonsignificant risk of cancer was evident (observed = 22, SMR = 111). No detailed breakdown of female cancer mortality was provided by the author.

In both male subcohorts, those hired before 1947 and those hired after 1947, an excess but nonsignificant risk of cancer of the bronchus was evident (observed = 45, SMR = 114; observed = 32, SMR = 134, respectively). No significant excess risk of prostate cancer occurred in either group (observed = 4, expected = 4.1; observed = 3, expected = 1.9, respectively). Even after consideration was given to the time since first employed, no significant excess risk was seen in workers who were alive 15 years after first employment but who had left the company in any of the following cause-of-death categories: all causes, combined cancer, cancer of the bronchus, and cancer of the prostate.

Upon further subdividing the cohort according to "exposed" versus "nonexposed" status, the author reported no significant excess risk due to prostate cancer (observed = 1, expected = 0.7) or cancer of the bronchus (observed = 10, expected = 8.3) in the "exposed" subcohort. The numbers became rather small, however, and as a consequence, the power of this study to detect a significant risk is diminished.

When consideration is given to length of employment and latency together, i.e., males formerly employed at the factory for less than 1 year and from 1 to 14 years but followed for over 15 years since the onset of employment, again no significant excess risk of bronchial cancer or prostate cancer is apparent. No information was provided concerning mortality in those workers with more than 14 years of employment in cadmium smelter work. The author concluded, on the basis of his analysis, that no evidence exists to suggest an increased risk of cancer mortality due to exposure to cadmium oxide dust.

Sorahan's analysis of latent effects included only terminated employees. Person-years of individuals still employed with the company were not enumerated, and only if the individual left the employment of the company (through death or other cause) were his person-years counted. This arrangement has the effect of altering the expected deaths by the non-inclusion of person-years of individuals who were at risk of death but who were still alive and working--an effect that could conceivably bias the SMRs. If differential mortality is considerable in the group still employed, as compared with the cohort, the extent of the bias might be even greater.

The study also suffers from the "healthy worker" effect brought about by the comparison of observed deaths with expected deaths based on the mortality rates of England and Wales. The SMRs are biased toward the null for all causes where the SMRs are greater than 100, while the deficit of deaths is increased in those cases where the SMRs are less than 100. Additionally, some 82 persons remain untraced with respect to their vital status, while 10 additional deaths were noted for which causes of death could not be found. The non-inclusion of the causes of death of the deceased members of this subgroup would tend to create a slight downward bias in the SMRs.

Furthermore, the tabular data presented classifies the cohort into two categories of exposure: "exposed" and "non-exposed," although in the "Population" section of the study, the author describes the jobs in the factories in terms of "high," "slight," and "minimal" exposure to cadmium. A clearer description is needed of how the three latter categories were reconstituted as "exposed" and "non-exposed" for the purposes of presenting the findings in tabular form. The author's treatment of the subject suggests that some portion of the study population received little exposure to cadmium. If this is so, perhaps these individuals should have been excluded from the study group. A better definition of intensity of exposure should have been utilized to present the tabular findings. It might have been more informative to present the tabular findings in terms of "high, "slight," and minimally" exposed subgroups, as described by the author in the text.

Overall, this paper presents no evidence of an increased risk of prostate cancer in cadmium-exposed workers. However, since several problems exist concerning the structure of the study, the diminishing sensitivity of the study in relation to certain highly exposed subgroups, and questionable evidence of exposure in a large portion of the cohort, the study cannot be said to provide conclusive evidence that cadmium is not carcinogenic.

Inskip and Beral (1982)

Inskip and Beral (1982) conducted a cohort motality study on residents of two small English villages, Shipham and Hutton, situated within seven miles of each other. Shipham is located in an area of substantial soil contamination by cadmium from the remains of a zinc mine that had operated on the site for nearly 400 years, until the middle of the nineteenth century. The village of Hutton was selected as a control. Investigations accomplished by the British Department of the Environment's Shipham Survey Committee revealed average garden soil cadmium levels ranging from 2 to 360 ug/g in the area, while national levels rarely exceeded 2 ug/g. Cadmium was believed to be absorbed in the diet mainly through the consumption of home-grown vegetables. According to a survey conducted by Thomas (1980), the dietary intake of cadmium in Shipham averaged 0.20 mg per week (range 0.04 to 1.08), while the national consumption averaged 0.14 mg per week (range 0.09 to 0.18).

Some 501 residents of Shipham and 410 residents of Hutton were entered into the cohort on September 29, 1939, and were followed until December 31, 1979, when SMRs were generated by cause of death. Data for both cohorts were compared with population statistics for England and Wales. Excess risks of mortality due to hypertensive and cerebrovascular disease and genitourinary disease were found in the Shipham residents. Cerebrovascular disease (observed = 65, SMR = 140, $P < 0.05$) was significantly high in residents of Shipham, especially females (observed = 44, SMR = 144, $P < 0.05$) and although the authors stated that a significant risk of genitourinary disease occurs only at $0.05 < P < 0.1$, recalculating the risk using the Poisson method gives a value of $P \leq 0.03$, for an SMR of 222 based on eight deaths, a statistically significant result that appears not to be due to chance alone.

Only two prostate cancer cases were observed in each village. Thus, SMRs were produced that do not differ significantly from those expected, although they were based on small numbers. With respect to lung cancer, no significant risks are evident, although the risk of lung cancer in females appears slightly elevated in both Shipham (observed = 4, SMR = 199) and Hutton (observed = 3, SMR = 181), based on small numbers.

The authors noted that overall mortality for these two rural communities is low compared to that of England and Wales, partially because of urban-rural confounding. They maintain that some evidence exists that cadmium influenced the "pattern of disease" in Shipham, specifically as regards kidney disease. On the other hand, the authors claim that the results do not support an association of cadmium and cancer or respiratory disease in cadmium-exposed persons. However, with respect to cause-specific cancer mortality, their data lack sensitivity because of diminishing power due to small numbers.

Another problem with this study, in addition to its low sensitivity is the lack of information concerning each person's actual exposure to cadmium. Although length of residence prior to 1939 could not be ascertained for individuals in the Shipham cohort, the authors were able to establish that all of the people studied in Shipham had lived there for at least 5 years. Furthermore, only 70% could be assigned to exposure categories based on the locations of their residences in areas of high or low cadmium content in the soils. Also, as the authors pointed out, the soil cadmium content, measured in 1974, may not accurately reflect exposures in 1939.

The greatest difficulty with this study, however, is in the knowledge that the average dietary consumption of cadmium in Shipham at 0.20 mg per week (range 0.04 to 1.08) was really not very different from the national average of 0.14 mg per week (range 0.09 to 0.18). The failure to find a detectable significant excess of cancer in Shipham residents may be due to a lack of sufficient dietary exposure to cadmium in Shipham residents. Furthermore, the presumption is that the cadmium was introduced through the gastrointestinal tract and not via the inhalation route, that the lung was not the target organ for cancer, and that therefore a significant excess of lung cancer would not be expected in this study. Hence, this paper should be judged inadequate with respect to the detection of a risk of lung or prostate cancer.

Andersson et al. (1982)

Anderssen et al. (1982) updated the earlier Kjellstrom et al. (1979) study by enlarging his cohort to 548 men and 101 women and requiring that cohort members have had a minimum of one year of cadmium exposure between 1940 and 1980 at only one alkaline battery factory in Oskarshamn, Sweden. Exposure levels were as described in the earlier Kjellstrom study, except that more recent data indicated that cadmium levels in the air generally fell below

20 ug/m^3, and that nickel levels were below 50 ug/m^3. Indeed, exposure to nickel seems to have been more prevalent in this factory than exposure to cadmium. Periods of exposure for members of the cohort ranged from 1 year to 52 years, with a median of 10 years. Twenty-five percent of the cohort were exposed for better than 22 years. Expected deaths were derived from cause-, calendar year-, and age-specific national rates of the Central Bureau of Statistics from 1951 to 1980. A total of 118 of the males died before 1981; the analysis was limited to deaths prior to age 80 because of the unreliability of death certificate data after age 79. The authors noted 103 deaths versus 122.6 expected, a deficit that was more than likely due to the "healthy worker" effect, and was confined mainly to cardiovascular disease (46 observed, 57.3 expected). If the analysis is limited to workers with a minimum exposure of 15 years, again a deficit occurs (50 observed, 58.4 expected). However, a significant increase in mortality due to nephritis and nephrosis was noted (3 observed, 0.41 expected, $P < 0.05$). A nonsignificant increase in the risk of prostate cancer was evident (3 observed, 2.5 expected).

The authors concluded that a causal relationship probably exists between earlier heavy cadmium exposure and the risk of renal disease, as well as a possible causal relationship with obstructive lung disease. The authors felt that one case of nasopharyngeal cancer was possibily due to exposure to nickel hydroxide, which is believed to cause nasal sinus cancer in man.

With regard to prostate cancer, the authors felt that their data suggested an increased risk--a finding that agrees with the earlier study by Kjellstrom et al. (1979). Because of this study's lack of sensitivity, however, nothing can be concluded from it with respect to lung cancer risks. Furthermore, latency was not evaluated in these workers. Useful data might have resulted if the lung cancer risk could have been evaluated without the requirement of a lengthy exposure. Former employees who worked less than 15 years, and who died from lung cancer many years later, could not be counted in tabulations in which 15 years of exposure were required for inclusion. The presence of nickel also precludes any definitive statement about the risk of cancer in these workers. For the above reasons, this paper must be judged inadequate for use in evaluating the risks of prostate cancer or lung cancer due to cadmium.

Kjellstrom (1982)

Kjellstrom (1982), in an updated historic prospective study of a cadmium nickel-battery factory, reported on mortality patterns in a cohort of 619 male employees (including 269 from an earlier study). During the study period from 1951 to 1980, 103 workers died, as compared to 126.4 expected on the basis of Swedish mortality statistics. The highest SMR was for urogenital disease, with 4 deaths versus 2.5 expected. This SMR is considered to be nonsignificant. Only 4 prostate cancer deaths occurred, versus 3.1 expected. The workers in this study cohort had a minimum of one year's exposure to cadmium. The author noted that, based on preliminary data, prostate cancer mortality was "more increased than the mortality due to other causes." This increase was not statistically significant, however.

The average historic exposure levels within this plant are depicted in Figure 1. From 1946 to 1976, there appears to have been a 1,000-fold drop in average exposure levels. A detailed analysis of past and present cadmium exposures in this factory has been published (Adamsson 1979). The author reports that nickel exposure levels have been at least the same as that of cadmium, and often as much as 10 times higher.

This study presents a number of problems. The records of employees terminated prior to 1945, a group in which the greatest risk is likely to be found, are nonexistent. Almost 31% of this group had exposures to cadmium of

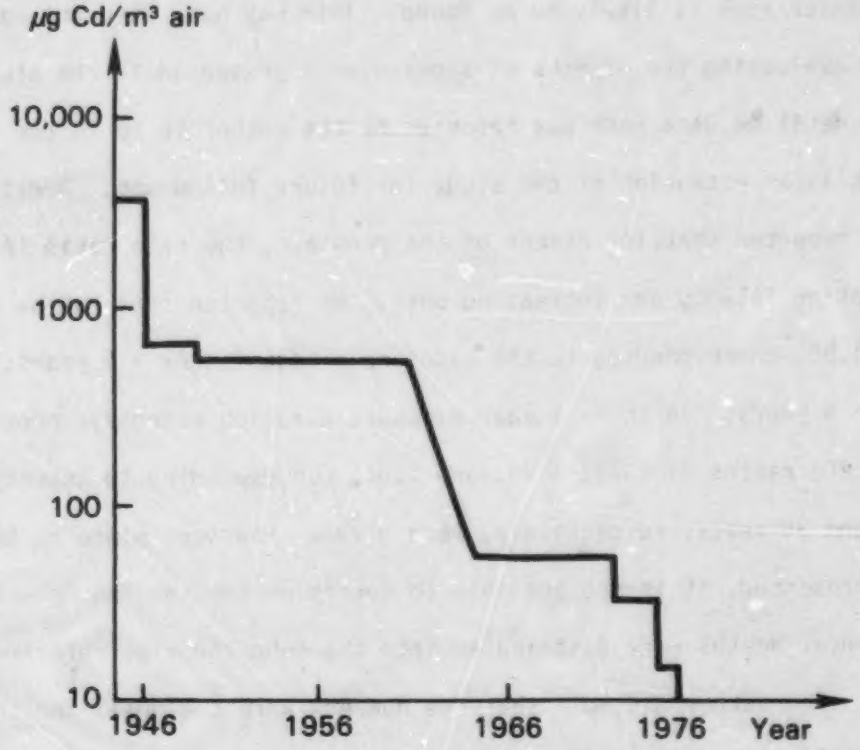

Figure 1. Concentration of cadmium in the air (ug Cd/m^3) from 1949 to 1976. Arithmetic mean of stationary and personal samples. (Kjellstrom 1982)

less than 2 years' duration. Almost 50% of the cohort (301 workers) received their first exposures to cadmium after 1959, which means that a large proportion of the cohort had not been followed even for 20 years, and thus, not enough time had elapsed for reliable evaluation of cancer risks. Furthermore, smoking information was not available for the older workers, a subgroup in which the greatest cancer risk is likely to be found. This may have been the reason why no results evaluating the effects of smoking were presented in the study, although a detailed data base was reported by the author to be in the development stages as an extension of the study for future follow-ups. Additionally, the author reported that for cancer of the prostate, the rate ratio increased with increasing latency and increasing dose. He reported rate ratios of 1.27, 1.33, and 1.55, corresponding to the exposure categories of > 0 years, > 1 year, and > 5 years. In the > 1 year exposure duration category, prostate mortality rate ratios of 1.33, 1.44, and 1.81, corresponding to latency periods of 1, 10, and 20 years, respectively, were given. However, since no tabular data were presented, it is not possible to determine how the four observed prostate cancer deaths were distributed into the subcategories referred to by the author. The author did note that the numbers were too small for the detection of statistically significant differences.

Kjellstrom repeated the analysis for urogenital diseases. For those with more than 20 years' exposure and 20 years' latency, 4 observed urogenital deaths occurred versus 0.93 expected ($P < 0.05$). This type of disease was found exclusively in the form of nephritis of the kidney. Again, it is difficult to conclude without evaluation that cadmium exposure was implicated, although the author himself stated that it is "clear that cadmium exposure increases mortality from kidney diseases" after high exposure intensity and long duration of exposure. The author noted a tendency in his data for a slightly increased nonsignificant risk of prostate cancer from exposure to cadmium.

In addition to the main study discussed above, Kjellstrom (1982) included discussions of three Japanese studies (Japan Public Health Association [JPHA] 1979, also reported by Shigematsu et al. 1981; Nogawa et al. 1978; and Nogawa et al. 1981) and a description of another ecological study planned by himself and the Department of Epidemiology at the University of Tokyo, for which only preliminary findings are available. In this latter study, age-standardized death rates in cadmium-polluted areas for persons 35-84 years of age were compared with the respective rates in non-cadmium-polluted areas. Preliminary data, according to Kjellstrom, suggested a nonsignificant tendency toward higher mortality rates in cadmium-exposed areas as compared with control areas (an age-adjusted mortality rate of 176 per 1,000 in cadmium-exposed areas versus 139 in the control areas). Prostate cancer and kidney disease mortality rates were also higher in the cadmium-exposed areas, but most of the prostate cancer mortality excess occurred in individuals 85 and over. No significant tests were done. This analysis was reported by Kjellstrom as tending to support the hypothesis of a cadmium effect, but "definite conclusions have to be left until all the analyses are completed."

Of the Japanese studies referred to by Kjellstrom (1982), the first (JPHA 1979, also reported by Shigematsu et al. 1981) was an analysis of cadmium exposure and mortality in the general environment. According to the author, people in many areas of Japan endure high cadmium exposures of up to several micrograms per day from consumption of contaminated rice. For each of four prefectures of Japan, age-standardized mortality rates were calculated in a cadmium-exposed area and compared to those calculated in a nonexposed reference area of the same prefecture. It was found that cancer mortality rates were generally about the same in the nonpolluted areas as in the polluted areas, but no significance tests were done. The only diseases for which death rates were found to be lower in the non-cadmium-polluted areas were kidney diseases and diabetes. With respect to prostate cancer mortality, two of the polluted areas had higher death rates than did the controls, while in two others the reverse was true. The author noted that the two prefectures with higher death rates of prostate cancer were the areas with the "highest likely cadmium exposure to the population." The former two prefectures tended to have higher rates of mortality from kidney disease and hyperplasia of the prostate as well. Because this was an ecological study, it can only be considered as suggestive of areas for future research.

The second Japanese study (Nogawa et al. 1978) found that in 2,689 men and women over age 50, the village-specific prevalence of low molecular weight proteinuria (LMWP) increased with an increase in the village-specific average cadmium concentration in rice. LMWP was measured by urinary retinol binding protein. It is very likely that this ecological study included persons who had never been exposed to cadmium in rice, as well as persons with prior-existing conditions, possibly introduced long before they were exposed to relatively high concentrations of cadmium in rice. The positive association noted by the author should not be construed to signify a causal association.

In the third study, Nogawa et al. (1981) conducted a mortality study of the 81 men and 124 women identified in the earlier study as having LMWP. They, along with the remaining men and women not found to have LMWP, were followed from 1974 to 1979. The authors found a nonsignificant ($P < 0.05$) twofold excess risk of death for men with LMWP and a nonsignificant 1.2-fold excess risk of death for women with LMWP. Mortality rates were based on 27 deaths of males with LMWP and 30 deaths of females with LMWP. A positive association of

LMWP with heart disease, cerebrovascular disease, nephritis, and nephrosis was noted. This association raises the specter of a possible confounding effect of hypertension with LMWP. If hypertension is a cause of LMWP, the higher mortality of the individuals that had LMWP may have been due to hypertension and not, as the author suggested, to cadmium exposure. The correlation with LMWP may thus be spurious, and hence, conclusions drawn from this study regarding an association of higher mortality with cadmium exposure must be characterized as certainly no more than suggestive.

Armstrong and Kazantzis (1983, 1982)

Armstrong and Kazantzis (1983) recently completed a cohort mortality study of 6,995 male cadmium workers born before 1940, who had had at least one year of employment during 1942-1970 in one of five British industries (primary production 64%; copper-cadmium alloy 8%; silver-cadmium alloy 14%; pigments and oxides 8%; and stabilizers 6%). The authors classified their cohort (derived from 17 major plants) into the following three categories of exposure: 1) "always low" (80%; 5,623 workers); 2) "ever medium" (17%; 1,173 workers); and 3) "ever high" (3%; 199 workers). Expected deaths were derived from SMRs based on mortality rates for the population of England and Wales. In addition, the authors referred to "approximately accounting" for regional variations in mortality by the use of cause-specific SMRs for standard regions published by the British Office of Population Censuses and Surveys during the period 1969-1973. This procedure is not completely described. The authors stated that in one instance they used the urban aggregate of a primarily rural region to derive SMRs for a plant that was situated in an urban portion of the region. The authors developed two-sided confidence intervals for significance testing through the use of the "exact" Poisson distribution method for some comparisons and the "normal" distribution for others.

Jobs were classified in the categories of high, medium, or low exposure to cadmium on the basis of discussions with hygienists and others with knowledge of past working procedures, taking into account biological or environmental monitoring results available.

Approximately 96% of this cohort was classified with a known vital status, whereas 4% either emigrated or were not traced. The authors excluded 38 deaths occurring to individuals 85 years of age or over. Presumably the authors ceased counting person-years for those live individuals who reached age 85 and over as well in order to retain comparability. The SMR for all causes of death was 97 (based on 1,902 deaths). The SMR for the first 10 years of followup was 79 (based on 205 observed deaths) and for later years 99 (based on 1,697 deaths), a phenomenon due most likely to the healthy worker effect. The authors found a significant excess of mortality due to bronchitis in the "ever high" exposure group, which appears to be dose-related (12 observed vs. 2.8 expected, $P < 0.01$) without regard for latency. This risk diminishes to a nonsignificant SMR of 138 in the "ever medium" group and finally to an SMR of 121 in the "always low" group, without regard for latent factors. Prostate cancer remained nonsignificant in all three exposure categories, without regard for latent factors. Because of the small numbers involved, however, the study could not detect a prostate cancer risk in the "ever high" exposure category. Although the authors stated that this cohort had been analyzed according to years since time of initial exposure, only the overall SMR was presented for those with 10 years or more of follow-up in the published version. No detailed tabular data were provided with respect to lung cancer or prostate cancer by time since onset of initial employment in the published results.

The authors agreed that the number of persons in the "ever high" exposure group (N = 199) was too small to preclude the possibility of the existence of a risk of prostate cancer from exposure to cadmium in this group. They further noted that no cases of prostate cancer turned up in the "ever medium" group, whereas 2.5 were expected. Prostate cancer was near to expected levels in the "always low" exposure group (23 observed, 20.4 expected) into which the large majority of the cohort fell. However, the authors provide no breakdown of site-specific cancer by time (10, 15, or 20 years) since onset of initial employment according to their three categories of exposure. Of interest is whether sufficient power remains in the study to detect a significant excess risk of prostate cancer in the latter two categories of exposure, particularly the "ever medium" group, 10, 15, or 20 years after the onset of exposure.

Furthermore, the possibility exists that when workers of 17 different plants are thrown together to form a massive cohort for study, some of these workers may have had little or no exposure to cadmium. If this occurred in the study under discussion, the likelihood of detecting a risk is reduced by the inclusion of person-years for individuals who essentially were not exposed to cadmium. This is especially true if there is a dose-response relationship operating in the cohort. Unless reliable criteria are established to quantify individual exposures to cadmium dust and compounds of cadmium, in addition to other confounding substances that may be present, it cannot be presumed that every member of this cohort was exposed to cadmium in high enough quantities to produce a detectable health risk. Furthermore, although some recent monitoring data may exist with which to quantify exposures, it is questionable that sufficient industrial exposure measurement data exist from the 1940s or 1950s and earlier to provide more than a guess at the levels of exposure to cadmium and other metals that existed when these persons were first employed. It may be that the historical prospective study design is not a sensitive enough analytical tool to be used in assessing cancer risks in a cohort of workers who, in general, were exposed to only "low" levels of cadmium. On the basis of the above factors, this study is seen to provide no evidence that cadmium is a powerful prostate cancer carcinogen.

On the other hand, although the risk of lung cancer overall was not significant (observed = 199, SMR = 107) without regard to intensity of exposure, the subgroup of workers who were employed for 10 or more years in low-exposure jobs exhibited a statistically significant excess risk of lung cancer (SMR = 126, observed = 100, $P < 0.05$). The authors, in an earlier draft of this paper (Armstrong and Kazantzis 1982), presented data concerning the lung cancer risk in workers having a minimum of 10 years' employment in the categories of "ever high" and "ever medium" exposure to cadmium. With respect to the "ever high" exposure category, no evidence exists of an elevated risk of lung cancer (SMR = 87, observed = 2) after 10 years' employment; however, little power remains with which to detect an elevated risk in that group. On the other hand, a suggestion of an elevated risk is apparent in the "ever medium" exposure group (SMR = 142, observed = 16) with 10 or more years of employment in the industry. It would have been valuable, however, to include a discussion of the lung cancer risk by longer time intervals since onset of exposure (i.e., 15 or 20 years). Power considerations probably would render such calculations of lung cancer risk in the "high" exposure subcohort and the "medium" exposure subcohort questionable.

The increased risk of lung cancer in the "always low" exposure category cannot be ascribed necessarily to cadmium exposure. It is generally accepted that manual workers smoke more than the general population; thus, it is not inconceivable that some of this increased risk is due to smoking. The authors state further that the absence of a gradient of risk with intensity of exposure makes it unlikely that the excess is due to cadmium. A full tabulation of SMRs in the three exposure intensity categories by time since onset of exposure

(10, 15, and 20 years) and similar duration of employment intervals might provide better dose-response information.

The exceptionally high risk of bronchitis in the "ever high" exposure group cannot be attributed to a cigarette smoking link because of the lack of a social-class gradient in the three exposure intensity categories. Although it is possible that other industrial pollutants may have contributed to this excess in the "ever high" exposure group, the authors point out that the size of the excess is much too great to be solely attributable to such confounding effects. Hence, they conclude that cadmium may have contributed to the excess of bronchitis.

Overall, this study did not sufficiently address the impact of latency and duration of exposure on the risk of prostate cancer, lung cancer, and hypertensive disease, i.e., because it considered only a single cut-off point (10 years). Perhaps additional tabulations that the authors state are in their possession can provide answers to the questions raised. While this study provides no evidence of a risk of prostate cancer, the possibility remains that at the exposure intensities indicated following a lapse of 10, 15, or 20 years from initial exposure, the historic prospective method may no longer be sensitive enough to detect a prostate cancer risk, if in fact one exists. A significant excess risk of lung cancer appears evident in workers with 10 years of "low" exposure to cadmium; however, this excess risk is not necessarily due to exposure to cadmium. Comparable data in the "ever medium" exposure group indicates a nonsignificant risk of lung cancer, but latency is not evaluated in sufficient detail. The data from the "ever high" group lack sufficient sensitivity to be judged adequate for the detection of a risk of lung cancer. It would be of interest to see if the addition of the 38 causes of death of persons over age 85 would alter the calculated risks. It might also be of some value to repeat the analysis on a plant-by-plant basis to determine which plants exhibit the highest risks by cause, and then develop exposure indices for those plants.

Nothing can be said on the basis of this study concerning the risk of hypertensive disease, except that it bears watching. However, the risk of bronchitis, which the authors conclude is probably due to exposure to cadmium dust, appears to be very significant. The dose-response relationship noted by the authors for bronchitis cannot entirely be attributed to confounding effects.

Sorahan and Waterhouse (1983)

Sorahan and Waterhouse (1983), in a recently published update of the earlier study by Sorahan (1981), employed a technique referred to as the "method of regression models in life tables (RMLT)" by Cox (1972) and Kneale et al. (1981) to test the null hypothesis that occupational exposure to cadmium is not associated with excess mortality. Only one set of mortality data was derived by means of calculating SMRs. Without qualification, only the risk of respiratory cancer was found to be statistically significant (observed = 89, expected = 70.2, $P < 0.05$). The risk of prostate cancer was elevated slightly but not significantly (observed = 8, expected = 6.6) in this phase of the study. These data, however, may not include one to four of the earlier prostate cancer cases found by Kipling and Waterhouse (1967), for the reasons stated below.

In the second part of their study, utilizing the RMLT, the authors prepared analyses with and without the four original cases included. The authors believed that only new cases of prostate cancer should be used to determine an RMLT-derived asymptotically normally distributed test-statistic measuring the significance of cancer of the prostate in their cohort. The potential confounders of sex, hiring date, age at hire, length of employment, and employment status were regressed against the test-statistic in order to eliminate the influence of these factors. Employment status was defined to be cumulative duration of employment in a "high" exposure job versus cumulative duration of employment in a "high or moderate" exposure job. Job categories were classified by exposure to cadmium as "high exposure," "moderate (or slight) exposure," and "minimal exposure." Only 8 jobs were considered to involve "high" exposure, while 14 were considered to involve "moderate (or slight)" exposure, and 53 were considered to involve "minimal exposure." With the four original cases included, the test-statistic (3.10, $P < 0.05$) remained statistically significant in the "highly" exposed group but remained nonsignificant (-0.32) when the original four cases were excluded. Even when reduction in exposure levels over calendar year periods was programmed into the analysis (assumed exposure levels from 1968 to 1972 were 40% of levels existing prior to 1967, and 10% post-1972) the test-statistic increased to 3.52 ($P < 0.01$) with the original four prostate cancers included. The authors, however, chose to note instead that "the effect of excluding the four previously reported cases of prostatic cancer is to reduce the statistically significant positive statistic to a small nonsignificant negative statistic." They concluded that "no new evidence has been produced which suggests an association between occupational exposure to cadmium and cancer of the prostate." Actually this conclusion may be unwarranted. One must wonder about the propriety of excluding persons who carry the disease in question from the study cohort if they fit the definition for inclusion. If these persons are to be excluded, such exclusion should be accomplished by redefining the study cohort so that selection biases do not creep into the results. This could perhaps be accomplished by defining a later time of initial employment.

The test-statistic generated for respiratory cancer in the "high-exposure" category in men is nonsignificant at 1.28, but for "high to moderately exposed" individuals, it is significant at 2.51 ($P < 0.05$). The authors suggested that exposures to the welding fumes of oxyacetylene found in jobs of "moderately exposed" workers might have accounted for this excess, which was chiefly confined to workers who began employment prior to 1940 (3.09, $P < 0.05$), to those who worked a minimum of 6 months (2.49, $P < 0.05$) and to those observed for 30 years or longer (3.18, $P < 0.05$). Minimally exposed workers who were also followed for 30 years or longer exhibited a significant test-statistic (2.36, $P < 0.05$). In no instance, did age, sex, year of starting employment, or years of follow-up produce a significant test-statistic for lung cancer in the group with the highest potential exposure to cadmium.

The authors pointed out the possibility that since job applicants with histories of lung and kidney disease were traditionally excluded from "high-exposure" jobs, this would tend to work against the demonstration of a potential hazard for related diseases in this category. They also indicated that since only 12% of their 599 deaths were in workers with more than 5 years' high-exposure employment, but 24% were in workers with moderate- or high-exposure employment of more than 5 years, this might explain why a significant statistic was not found for lung cancer in the "high" exposure group if, in fact, occupational exposure to cadmium oxide is a risk factor. Presumably, this differential mortality may indicate a lack of sensitivity in the "highly" exposed group due to small numbers. If such a risk dose not exist in truth, the explanation for the seemingly inverse dose-response effect may be due to exposure to oxyacetylene welding fumes, exposure to nickel hydroxide dust, or to chance alone.

The authors felt also that although information on their cohort's smoking habits was not available, if smoking were the reason for an excess of respiratory cancer, then similar associations should be expected for diseases of the circulatory system, and such associations were not found. The authors stated that the analysis could not differentiate between exposure to cadmium oxide dust and exposure to nickel hydroxide because almost every job with high cadmium exposure also had high nickel exposure.

In conclusion, Sorahan and Waterhouse (1983) found an increased risk of prostate cancer that was entirely dependent on the original four cases of Kipling and Waterhouse (1967), but found no association with prostate cancer for cases subsequent to these. They also found an increased risk of respiratory cancer among workers moderately or highly exposed to cadmium oxide dust and initially employed before 1940--a finding which was confounded by exposures to oxyacetylene welding fumes and to nickel hydroxide dust.

Varner (1983, unpublished)

ASARCO Inc., the owners of the cadmium smelter that had been studied by Lemen et al. (1976), updated that study with one of their own (Varner 1983, unpublished) in which all employees were included who had had at least six months' employment at the smelter between January 1, 1940 and December 31, 1969. The size of the cohort was enlarged to 644. This very preliminary report was accompanied by a letter to David Bayliss of the CAG from Lowell White of ASARCO, January 11, 1984, in which White indicated that the follow-up for this study would extend to the end of 1981. According to the letter, the National Institute for Occupational Safety and Health (NIOSH) staff scientists, in a cooperative arrangement, agreed to provide follow-up services on all members of this cohort, and to provide copies of death certificates to ASARCO in exchange for available work history and biological monitoring data.

As in the Lemen et al. (1976) study, Varner (1983) used a methodological technique called the Standardized Case Ratio (SCR), which is analogous to the calculation of SMRs, with the exception that expected deaths for particular causes of death are derived by dividing age- and cause-specific attributable deaths by total deaths in the age and year category corresponding to each particular decendent's age and year of death. The resulting proportions are summed to arrive at the number of expected deaths. These methods are still under peer review, according to White (letter to David Bayliss, CAG, January 11, 1984) and cannot yet be considered reliable.

The preliminary findings of Varner (1983) differed from the Lemen et al. (1976) study in that the risk of prostate cancer was found to be no longer statistically significant, although it was still elevated (observed = 5, SCR = 169)*, while the risk of lung cancer remained statistically significant (observed = 23, SCR = 163). The author attributed the excess risk of lung cancer to several factors: increased cumulative exposure to cadmium, years of exposure, age at death, latent period, and/or cigarette smoking.

The author maintains that a "substantially higher than normal prevalence of heavy cigarette smoking" in a subcohort of the main study cohort may have contributed to "part or all" of the increased lung cancer incidence. Other findings include a significant risk of urinary tract cancer (observed = 6, SCR = 252, $P = < 0.05$); specific bladder cancers (observed = 5, SCR = 374, $P < 0.01$); total cancer (observed = 53, SCR = 126, $P < 0.05$); nonmalignant respiratory disease (observed = 7, SCR = 153, $P < 0.05$); ulcer of the stomach and duodenum (observed = 7, SCR = 452, $P < 0.01$); and accidents (observed = 19, SCR = 150; $P < 150$, $P < 0.05$). However, the findings also reflect a significant deficit of deaths due to heart disease (observed = 68, SCR = 77, $P < 0.01$) and stroke (observed = 6, SCR = 40, $P < 0.05$).

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*SCR (Standardized Case Ratio) is analogous to the Standard Mortality Ratio, differing in that expected deaths for a specific cause were derived by dividing age- and cause-specific attributable deaths by total deaths in the age and year of death category of each decedent. The resulting proportions are summed to obtain expected deaths. These methods are under peer review, according to White (January 11, 1984).

Calculated cumulative exposure to cadmium (mg-years/m^3) was determined for every member of the cohort on the basis of personal monitoring measurements made during the period 1973-1976. The author pointed out that this variable assumes that exposures over several decades were about the same. The author felt that such a procedure tends to underestimate exposures of many years ago when cadmium levels were probably higher, while at the same time tending to overestimate exposures of recent years.

Varner (1983) found that a dose-response relationship existed with respect to lung cancer, and to a lesser degree, total malignant neoplasms, as follows:

Exposure	Lung cancer		Malignant neoplasms	
(mg-years/m^3)	Observed	SCR	Observed	SCR
0-4	7	95	23	108
5-15	6	159	14	123
16+	10	332 ($P < 0.01$)	16	168

Lung cancer was also found to be related to smoking in the following manner:

Pack-years	Observed	SCR
Unknown	10	115
Nonsmokers	0	---
1-19	2	183
19	11	313 ($P < 0.01$)

No such effects were seen for bladder cancer.

With respect to lung cancer, the author reports that 77.5% of the cadmium workers had been smokers, and that 53.2% had smoked the equivalent of one pack a day for 20 years. In a 1970 Household Interview Survey by the National Center for Health Statistics, it was reported that 69.2% of blue collar workers had smoked a pack or more of cigarettes a day at some time in their lives. Thus, some evidence exists for a confounding effect due to cigarette smoking, since the proportion of smokers in the Varner (1983) cohort was somewhat greater than that shown by survey data.

In the letter attached to this preliminary paper, Dr. White cautioned that several problems had to be solved concerning the validity of the study's findings, not the least of which involved the credibility derivation of SCRs. The NIOSH update of the Lemen et al. (1976) study, which is reviewed later in this section, also contains 60 fewer individuals, who were allegedly excluded by NIOSH for "various reasons" upon which Varner does not elaborate. Varner included all individuals "regardless of exposure."

Another problem with the study is that the death certificates were received only 2 weeks prior to the presentation of the paper at the 4th International Cadmium Conference, thus necessitating the use of cause-of-death codes that appeared on the death certificates as they were received. Both the NIOSH cause-of-death codes and the state's cause-of-death codes are described as differing. White referred to the presence of what he termed "nosology bias" in the ascertainment of underlying causes of death. He states that some 93 death certificates were coded by a different nosologist than the one who performed the coding for the preliminary report, leading to 21 distinctly different cause of death codes. The authors are seeking a neutral "unbiased" method for coding death certificates prior to the issuance of a final report on the study. Furthermore, White believes that the possible presence of confounding variables as an explanation for elevated risks, especially of lung cancer, has not been properly or completely addressed in this preliminary report. White reported that Michael Thun and his coworkers at NIOSH (Thun et al. 1984) have attempted to account for the contribution of arsenic exposure and cigarette smoking in their study, which is reviewed below. Additionally, White reported that the follow-up through 1981 was incomplete, although the percentage remaining with an unknown vital status was not given. He reported that ASARCO, Inc. recently contracted with the Social Security Administration to provide vital status information, and that it is hoped that the "final procurement" of death certificates for the study can begin soon (presumably after the date of his letter of January 11, 1984). The cohort has been expanded, and a number of newly found personnel records have been included for evaluation in the final report.

Because of the very preliminary nature of the Varner (1983) study in its present form, the results will not be prejudged here. Although the author found a dose-related significant excess risk of lung cancer, as he explains, this may be due in part to the confounding effects of smoking and/or arsenic exposure. Additionally, although the risk of prostate cancer is elevated, it is no longer statistically significant. Whether the final version of the study will sustain such a finding is not presently clear, in view of the many problems that must be solved. It does not appear at this time that the final version of the study will be forthcoming in the very near future.

Hence, the Varner study cannot, at present, be used either to substantiate an excess risk of lung cancer due to cadmium exposure or to refute the earlier findings of significant prostate cancer in the Lemen et al. study.

Thun et al. (1984, unpublished)

In a separate enlargement and update of the Lemen et al. (1976) study, Thun et al. (1984, unpublished) broadened the cohort to include white males who worked a minimum of 6 months in production work during the period 1940-1969. The resulting 612 members were followed an additional 5 years to the end of 1978. The difference between the size of the Varner (1983) cohort of 644-612 = 32 and the Thun et al. (1984) cohort is not completely explained, but may consist of non-production employees such as guards, office workers, and office area janitors. Cause-specific mortality rates for seven causes of death were compared between the cohort and U.S. white males. Death certificates were coded by a qualified nosologist according to the protocol of the version of the International Classification of Diseases (ICD) in effect at the time of death. Expected deaths were calculated using the life-table system developed by NIOSH. The risk of lung cancer (observed = 20, SMR = 265, $P < 0.05$) was significantly in excess in workers employed for 2 or more years before and after the cessation of arsenic smelting in 1925. Prostate cancer was no longer excessive in these workers.

From Table 16, it can be seen that air exposure measurements chronologically decreased with the introduction of a mandatory respiratory program introduced in the 1940s. The estimates in Table 16 are based on area monitoring data, adjusted to reflect actual exposures during the wearing of respirators. The source of the data--the plant's personnel records--provided enough detail so that broad job categories could be assigned to each period of a worker's employment.

The plant studied has produced cadmium metals and cadmium compounds from 1925 to the present. It had been an arsenic smelter from 1918 to 1925, and a lead smelter from 1886 to 1918. Urine cadmium data, which were available for 261 members of the cohort employed beyond 1960, suggested a highly exposed population. Since arsenic is a known lung carcinogen, the authors separated arsenic-exposed workers from the rest of the cohort by dividing their cohort into two subgroups, those employed on or before January 1, 1926, and those employed after that date. In the first group, 4 lung cancer deaths were observed versus 0.56 expected, while in those employed 2 years or longer after January 1, 1926, 16 observed lung cancer deaths were observed versus 6.99 expected, $P < 0.05$. Directly standardized rate ratios (SRRs) for these data exhibit a constant twofold increase in lung cancer mortality with longer duration of employment (Table 17). The authors state that a similar pattern results when the indirectly standardized mortality ratios are stratified for latency.

TABLE 16. ESTIMATES OF INHALATION EXPOSURES (mg/m^3) BY PLANT DEPARTMENT AND TIME PERIOD (Smith et al. 1980)[a]

Time Period	Sampling	Roaster	Mixing	Calcine	Solution	Tankhouse[b]	Foundry	Retort	Pigment	Office and Lab[c]
Pre-1950	1.0	1.0	1.5	1.5	0.8	0.04	0.8	1.5	0.2	0.02
1950-1954	0.6	0.6	0.4	1.5	0.8	0.04	0.1	0.2	0.2	0.01
1955-1959	0.6	0.6	0.4	1.5	0.4	0.04	0.1	0.2	0.04	0.01
1960-1964	0.6	0.6	0.4	0.4	0.4	0.02	0.1	0.2	0.04	0.007
1965-1976	0.6	0.6	0.4	0.15	0.04	0.02	0.04	0.2	0.04	0.007

[a] Estimated inhalation exposures cccurred in various departments and were based on area monitoring data adjusted to reflect the actual exposures of workers wearing respirators.

[b] Tankhouse estimates were also used for non-production plant departments (e.g., repair shops) that were not measured directly.

[c] Office estimates were also used for non-plant areas (e.g., the plant guard) that were not measured directly.

TABLE 17. LUNG CANCER (ICD 162-163) MORTALITY BY DURATION OF EMPLOYMENT, WHITE MALES HIRED ON OR AFTER 1/1/26

(Thun et al. 1984)

Duration of employment	No. of deaths	Mortality rate[a]	SRR[b]
6-23 months	0	0	-
2-9 years	9	15.73	2.2
10-19 years	3	14.28	2.0
20+ years	4	16.28	2.2
U.S. white males	-	7.27	1

[a] Rate x 10,000 person-years was directly standardized for age and calendar time to the person-years distribution of the overall cadmium cohort.

[b] Standardized rate ratio (SRR) is the directly standardized mortality rate of subgroup/summary rate for U.S. white males.

With respect to arsenic exposure, even after 1925, the author states that a small and unspecified number of workers processed arsenic intermittently in one area of the plant. This lasted into the 1930s. A second continuing source of arsenic exposure came in the sampling, mixing, roasting, and calcine furnace areas. Six industrial hygiene measurements in 1950 showed arsenic concentrations ranging from 300 to 700 ug/m^3 in the vicinity of the roasting and calcine furnaces, the highest measurement anywhere in the plant. The authors report that later measurements by the company and the U.S. Occupational Safety and Health Administration (OSHA), in 1979, indicate a decrease in arsenic concentration to 100 ug/m^3 in this area. However, the author points out that although air levels of arsenic in this specified area were 10 times the OSHA threshold of 10 ug/m^3, the personal exposures of individuals in this area were lower because of respirator usage--a practice that had been in effect since 1940. In fact, on the basis of a "most-likely-case" scenario, the authors estimate that the average arsenic exposure of persons in this study would have been 25 ug/m^3 under the following conditions:

(1) the average airborne arsenic exposure was 500 ug/m^3 in the high-arsenic work areas;

(2) there was a respiratory protection factor of 75%; and

(3) 20% of the person-years of exposure were spent in such areas (based on personnel and biological monitoring data).

Hence, according to the authors, if the 586 workers hired after 1926 were employed an average of 3 years, they would have acquired 1,758 person-years of exposure to 25 ug/m^3 of arsenic. Based on an OSHA risk assessment model for arsenic (OSHA 1983), such an exposure should have resulted in no more than 0.78 lung cancers. The authors feel that the 25 ug/m^3 figure overestimates actual exposures because only a fraction of jobs in the "high-arsenic" areas involved exposures as high as those in the furnace areas. High-exposure jobs in the roaster area were frequently staffed by entry-level workers with less than 6 months' employment, who would for that reason never qualify for inclusion in the study, although the authors included them in their estimate that 20% of the person-years of exposure were in "high-arsenic" jobs. Furthermore, the authors point out that urinary arsenic levels from 1960 to 1980 averaged 46 ug/L, which is consistent with an inhaled arsenic concentration of 14 ug/m^3. If one assumes an average inhaled concentration of 125 ug/m^3 (25% of 500 ug/m^3) over 3 years, a ninefold overestimate of exposure results, which more than offsets the unquantified high exposures during the early years. Based on the above analysis, the authors concluded that arsenic alone could not explain the observed excess of lung cancer deaths in this cohort.

With respect to cigarette smoking, information concerning the smoking habits of 70% of the cohort was obtained from survivors and next-of-kin.

Some 77.5% for whom information was available were current or former smokers. This prevalence of "ever" smokers is close to the 72.9% prevalence noted among white males over 20 in the 1965 Health Interview Survey referred to previously. The authors pointed out that even if the percentage of heavy smokers (25+ cigarettes/day) in the cadmium cohort were double that of the 20% white male 1965 population, the rate ratio would increase by only 1.25, according to the method of Axelson (1978). Hence, the authors conclude that cigarette smoking is unlikely to account for the twofold increase in lung cancer deaths observed among workers in this cohort with 2 or more years or employment.

The authors also note the lack of a clear dose-response relationship--a situation which they suggest could be an artifact of using length of employment as a surrogate for dose. They point out that, in plants such as the one studied, one of the privileges of seniority is that long-term workers can bid into more desirable, less exposed jobs, and that for this reason, the use of data on duration of employment can lead to overestimation of exposure in long-term workers.

Of concern in this study is the possibility that the combined effect of increased cigarette smoking and exposure to arsenic might have served to produce the significant positive risk of lung cancer observed in this cohort. This possibility is all the more distinct because the risk of lung cancer in the study was not seen to be overwhelming. A subtle combination of factors such as the ones mentioned above could conceivably have served to produce the excess risks found, even though such an eventuality is unlikely. Thus, although this study cannot be said to be conclusive with respect to risks of lung cancer from exposure to cadmium, it constitutes the most clear-cut evidence yet leading to this conclusion.

Summary

Of the many epidemiologic studies of cancer in cadmium-exposed persons reviewed by the CAG, only four (Kipling and Waterhouse 1967, Lemen et al. 1976, Holden 1980, and Sorahan and Waterhouse 1983) provide evidence of a statistically significant positive association ($P < 0.05$) of cadmium with prostate cancer.

Several other studies (Potts 1965; Kjellstrom et al. 1979; McMichael et al. 1976a, b; Anderssen et al. 1982; Kjellstrom 1982; Varner 1983, unpublished; and Thun et al. 1984, unpublished) provide the suggestion of an increased risk of prostate cancer (although statistically nonsignificant) with exposure to cadmium.

With respect to these studies, however, several comments are in order. The studies by Potts (1965), Kipling and Waterhouse (1967), Sorahan (1981), and Sorahan and Waterhouse (1983) cannot be considered independently of one another. The workers in the McMichael et al. (1976a, b) studies were subsequently shown not to have had any exposures to cadmium, and the observed excess of prostate cancer in this study was felt by Monson and Fine (1978) and Goldsmith et al. (1980) to be due to other, unexplained factors at the companies studied.

Furthermore, the significant excess risk of prostate cancer in the Lemen et al. (1976) study dropped to a nonsignificant excess risk in both of the updated versions of that study (Varner 1983 and Thun et al. 1984). Kjellstrom's "corrected healthy worker effect" risk ratio of 2.4 is nonsignificant because of the small numbers involved, although it approaches borderline significance at $P < 0.09$, offering the suggestion of a possible association of prostate cancer with cadmium exposure.

Two other studies (Humperdinck 1968 and Holden 1969) did not report evidence of an association of prostate cancer with cadmium exposure, chiefly because the comparison population was either inadequate for the assessment of risk (Humperdinck) or absent entirely (Holden).

An update by Kjellstrom (1982) of his earlier 1979 study again failed to demonstrate a significant risk of cancer of the prostate due to cadmium. One of the failings of this study was that members of the cohort were not observed long enough to permit the evaluation of latent effects. More than half of the cohort had received no exposure to cadmium prior to 1959, and thus could not have been followed even for 20 years.

The study by Armstrong and Kazantzis (1983) of 6,994 workers also failed to demonstrate an increased risk of prostate cancer due to cadmium. This study combined cohorts from 15 different plants, each with its own unique exposure history, and none of which were necessarily comparable. Exposures to cadmium in most of these plants may have been below the level at which the study design could detect a risk.

Kolonel (1976) found a statistically significant elevated risk of renal cancer in persons occupationally exposed to cadmium, and an even greater risk in occupationally exposed people who smoke, thus raising the possibility of a synergism. The chance of selection bias and concurrent occupational exposures to nickel, lead, zinc, and a variety of metals also minimizes the importance of the findings.

With respect to a risk of prostate cancer from exposure to cadmium and its compounds, the evidence is weak at best, and is considered by the CAG to be insufficient to conclude that cadmium is a prostate carcinogen.

On the other hand, recent evidence from the same studies seems to provide better evidence of a lung cancer risk from exposure to cadmium. Strong evidence is available from the Thun et al. (1984) study that the significant twofold excess risk of lung cancer seen in cadmium smelter workers is probably not due to the presence of arsenic in the plant or to increased smoking by such workers. Thun et al. analyzed both factors as potential confounders and convincingly dismissed both in this updated and enlarged version of the earlier Lemen et al. (1976) study, which also demonstrated a significantly elevated risk of lung cancer.

Varner (1983) also found a statistically significant excess of lung cancer in his updated enlarged version of the earlier Lemen et al. study. But unlike Thun et al., Varner noted a dose-response relationship for both lung cancer and total malignant neoplasms with increasing cumulative exposure. Varner indicated that the significant excess is probably due to the smoking factor or to the presence of arsenic in the plant. However, he had not had a chance to analyze their impact because his paper was preliminary.

Sorahan and Waterhouse (1983), using the SMR method, also noted a clearly statistically significant risk of lung cancer in their study population. In addition, a significantly high test-statistic was noted for excess lung cancer utilizing the "regression models in life tables (RMLT)" method in the "high to moderately exposed" group but not in the "highest exposure" category, although the test-statistic was elevated. Sorahan suggested that the excess might be due to exposure to fumes from oxyacetylene welding. No significantly high test-statistic was found in his "highest exposure" group, however, possibly because of a lack of sensitivity due to small numbers.

In his earlier paper, Sorahan (1981) found the risk of lung cancer to be nonsignificantly elevated through SMRs calculated in a retrospective/prospective cohort study of workers who began employment before and after the amalgamation of two factories into a nickel-cadmium battery plant.

Armstrong and Kazantzis (1983) also demonstrated a significant risk of lung cancer in workers designated by them as having worked in "low exposure" jobs for a minimum of 10 years. Little sensitivity remained in the "highly exposed" group with which to detect a risk after a minimum of 10 years' employment, and such a significant risk was not shown. Furthermore, only a suggestion of an excessive risk was evident in the "ever mediumly" exposed group in workers with a minimum of 10 years' employment. This study, however, did not deal with latent factors 15 or 20 years after initial exposure in combination with length of employment in sufficient detail. Also, 17 different plant populations were combined to form one cohort study, thus raising the possibility that very little exposure occurred to most members of the cohort.

Holden (1980) reported a significantly excessive risk of lung cancer in "vicinity" workers, which he maintained could have been due to the presence of other metals, such as arsenic. No excess risk was seen in the group with the highest exposure, however. Latent factors were not considered, nor was the movement of workers from jobs with high exposure to jobs with low exposure, possibly because of seniority.

Anderssen et al. (1982), in their update of the Kjellstrom et al. (1979) study, noted a slight but nonsignificant lung cancer risk in alkaline battery factory workers; however, this observation was based on only three lung cancer deaths occurring to this cohort, and the study also suffers from a "small numbers" problem. In the earlier study, Kjellstrom et al. (1979) observed a slight but nonsignificant excess of lung cancer based on two cases in the same small group of cadmium-nickel battery factory workers.

Inskip and Beral (1982) noted a slightly increased but nonsignificant risk of lung cancer among female residents of two small English villages who presumably were exposed to cadmium-contaminated soil via the oral route. However, again only a small number of lung cancers were observed.

Overall, the weight of human epidemiologic evidence is suggestive of a significant risk of lung cancer from exposure to cadmium and/or cadmium oxide, although the human evidence is not compelling with respect to finding cadmium to be a strong lung carcinogen. At best, the epidemiologic evidence of the carcinogenicity of cadmium must be described as limited, according to the criteria of the IARC.

QUANTITATIVE ESTIMATION

INTRODUCTION

This quantitative section deals with the unit risk for cadmium in air and the potency of cadmium relative to other carcinogens that the Carcinogen Assessment Group (CAG) has evaluated. The unit risk estimate for an air pollutant is defined as the lifetime cancer risk occurring in a hypothetical population in which all individuals are exposed continuously from birth throughout their lifetimes to a concentration of 1 ug/m^3 of the agent in the air that they breathe. These calculations are done to estimate in quantitative terms the impact of the agent as a carcinogen. Unit risk estimates are used for two purposes: 1) to compare the carcinogenic potencies of several agents with each other, and 2) to give a crude indication of the population risk that would be associated with air or water exposure to these agents, if the actual exposures were known.

The data used for quantitative estimation are taken from one or both of the following: 1) lifetime animal studies, and 2) human studies where excess cancer risk has been associated with exposure to the agent. In animal studies it is assumed, unless evidence exists to the contrary, that if a carcinogenic response occurs at the dose levels used in the study, then response will also occur at all lower doses with an incidence determined by the extrapolation model.

There is no solid scientific basis for any mathematical extrapolation model that relates carcinogen exposure to cancer risks at the extremely low concentrations that must be dealt with in evaluating environmental hazards. For practical reasons, such low levels of risk cannot be measured directly either by animal experiments or by epidemiologic studies. We must, therefore, depend on our current understanding of the mechanisms of carcinogenesis for guidance as to which risk model to use. At the present time the dominant view of the carcinogenic process involves the concept that most cancer-causing agents also cause irreversible damage to DNA. This position is reflected by the fact that a very large proportion of agents that cause cancer are also mutagenic. There is reason to expect that the quantal type of biological response, which is characteristic of mutagenesis, is associated with a linear nonthreshold dose-response relationship. Indeed, there is substantial evidence from mutagenicity studies with both ionizing radiation and a wide variety of chemicals that this type of dose-response model is the appropriate one to use. This is particularly true at the lower end of the dose-response curve; at higher doses, there can be an upward curvature, probably reflecting the effects of multistage processes on the mutagenic response. The linear nonthreshold dose-response relationship is also consistent with the relatively few epidemiologic studies of cancer responses to specific agents that contain enough information to make the evaluation possible (e.g., radiation-induced leukemia, breast and thyroid cancer, skin cancer induced by arsenic in drinking water, liver cancer induced by aflatoxins in the diet). Some supporting evidence also exists from animal experiments (e.g., the initiation stage of the two-stage carcinogenesis model in rat liver and mouse skin). Linearity is also supported when the mode of action of the carcinogen in question is similar to that of the background cancer occurrence in the exposed population.

Because its scientific basis, although limited, is the best of any of the current mathematical extrapolation models, a linear nonthreshold model has been adopted as the primary basis for estimating risk at low levels of exposure. The risk estimates made with this model should be regarded as conservative, representing the most plausible upper limit for the risk, i.e., the true risk is not likely to be higher than the estimate, but it could be lower.

For several reasons, the unit risk estimate based on animal bioassays is only an approximate indication of the absolute risk in populations exposed to known carcinogen concentrations. First, there are important species differences in uptake, metabolism, and organ distribution of carcinogens, as well as species differences in target site susceptibility, immunological responses, hormone function, dietary factors, and disease. Second, the concept of equivalent doses for humans compared to animals on a mg/surface area basis is virtually without experimental verification regarding carcinogenic response. Finally, human populations are variable with respect to genetic constitution and diet, living environment, activity patterns, and other cultural factors.

The unit risk estimate can give a rough indication of the relative potency of a given agent as compared with other carcinogens. Comparative potency estimates for different agents are more reliable when the comparisons are based on studies in the same test species, strain, and sex, and by the same route of exposure, preferably inhalation.

The quantitative aspect of carcinogen risk assessment is included here because it may be of use in the regulatory decision-making process, e.g., in setting regulatory priorities, evaluating the adequacy of technology-based controls, etc. However, it should be recognized that the estimation of cancer risks to humans at low levels of exposure is uncertain. At best, the linear extrapolation model used here provides a rough but plausible estimate of the upper limit of risk. The risk estimates presented in subsequent sections should not be regarded as accurate representations of the true cancer risks even when the exposures are accurately defined. However, the estimates presented may be factored into regulatory decisions to the extent that the concept of upper risk limits is found to be useful.

The mathematical formulation chosen to describe the linear nonthreshold dose-response relationship at low doses is the linearized multistage model. This model employs enough arbitrary constants to be able to fit almost any monotonically increasing dose-response data, and it incorporates a procedure for estimating the largest possible linear slope (in the 95% confidence limit sense) at low extrapolated doses that is consistent with the data at all dose levels of the experiment.

In addition to the multistage model currently used by the CAG for low-dose extrapolation (a detailed description of the procedure is given in Appendix B), three more models, the probit, the Weibull, and the one-hit, are employed for purposes of comparison. These models cover almost the entire spectrum of risk estimates that could be generated from the existing mathematical extrapolation models. The models are generally statistical in character and are not derived from biological arguments, except for the multistage model, which has been used to support the somatic mutation hypothesis of carcinogenesis (Armitage and Doll 1954, Whittemore 1978, Whittemore and Keller 1978).

The main difference among the above models is the rate at which the response function P(d) approaches zero or P(0) as dose d decreases. For instance, the probit model would usually predict a smaller risk at low doses than the multistage model because of the difference of the decreasing rate in the low-dose region. However, it should be noted that the multistage model could always be artificially made to have the same (or even greater) rate of decrease as the probit model, by making some dose transformation and/or by assuming that some of the parameters in the multistage model are zero. This, of course, is not reasonable without knowing, a priori, what the carcinogenic process for the agent is.

Although the multistage model appears to be the most reasonable or at least the most general model to use, the point estimates generated from this model are of limited value because of uncertainty as to the shape of the dose-response curve beyond the experimental exposure levels. Furthermore, the point estimates at low doses extrapolated beyond the experimental dose could be extremely unstable and could differ drastically, depending on the size of the lowest experimental dose. Since the upper-bound estimates at low doses from the multistage model are relatively more stable than the point estimates, the CAG suggests that the upper-bound estimate of the risk (or the lower-bound estimates of the dose) be used in evaluating the carcinogenic potency of a suspect carcinogen. The upper-bound estimate can be taken as a plausible estimate if the true dose-response curve is actually linear at low doses. The upper-bound estimate means that the risks are not likely to be higher but could be lower if the compound has a concave upward dose-response curve or a threshold at low doses. Another reason why, at best, only an upper-bound estimate of the risk can be obtained when animal data are used is that the estimated risk is no more than conditional probability under the assumption that an animal carcinogen is also a human carcinogen. Therefore, in reality, the actual risk could range from a value near zero to an upper-bound estimate.

PROCEDURES FOR DETERMINING CARCINOGENIC POTENCY

Description of the Low-Dose Animal Extrapolation Model

Let P(d) represent the lifetime risk (probability) of cancer at dose d. The multistage model has the form

$$P(d) = 1 - \exp\left[-(q_0 + q_1 d^2 + \ldots + q_k d^k)\right]$$

where

$$q_i \geq 0, \; i = 0, 1, 2, \ldots, k$$

Equivalently,

$$P_t(d) = 1 - \exp[-(q_1 d + q_2 d^2 + \ldots + q_k d^k)]$$

where

$$P_t(d) = \frac{P(d) - P(0)}{1 - P(0)}$$

is the extra risk over background rate at dose d or the effect of treatment.

The point estimate of the coefficients q_i, $i = 0, 1, 2, \ldots, k$, and consequently the extra risk function $P_t(d)$ at any given dose d, is calculated by maximizing the likelihood function of the data.

The point estimate and the 95% upper confidence limit of the extra risk $P_t(d)$ are calculated by using the computer program GLOBAL79, develped by Crump and Watson (1979). At low doses, upper 95% confidence limits on the extra risk and lower 95% confidence limits on the dose producing a given risk are determined from a 95% upper confidence limit, q_1^*, on parameter q_1. Whenever $q_1 > 0$, at low doses the extra risk $P_t(d)$ has approximately the form $P_t(d) = q_1^* \times d$. Therefore, $q_1^* \times d$ is a 95% upper confidence limit on the extra risk, and R/q_1^* is a 95% lower confidence limit on the dose producing an extra risk of R. Let L_0 be the maximum value of the log-likelihood function. The upper limit, q_1^*, is calculated by increasing q_1 to a value of q_1^* such that when the log-likelihood is remaximized subject to this fixed value q_1^* for the linear coefficient, the resulting maximum value of the log-likelihood L_1 satisfies the equation

$$2(L_0 - L_1) = 2.70554$$

where 2.70554 is the cumulative 90% point of the chi-square distribution with one degree of freedom, which corresponds to a 95% upper-limit (one-sided). This approach of computing the upper confidence limit for the extra risk $P_t(d)$

is an improvement on the Crump et al. (1977) model. The upper confidence limit for the extra risk calculated at low doses is always linear. This is conceptually consistent with the linear nonthreshold concept discussed earlier. The slope, q_1^*, is taken as an upper bound of the potency of the chemical in inducing cancer at low doses. (In the section calculating the risk estimates, $P_t(d)$ will be abbreviated as P.) In fitting the dose-response model, the number of terms in the polynomial is chosen equal to (h-1), where h is the number of dose groups in the experiment, including the control group.

Whenever the multistage model does not fit the data sufficiently well, data at the highest dose is deleted, and the model is refit to the rest of the data. This is continued until an acceptable fit to the data is obtained. To determine whether or not a fit is acceptable, the chi-square statistic

$$X^2 = \sum_{i=1}^{h} \frac{(X_i - N_i P_i)^2}{N_i P_i \ (1-P_i)}$$

is calculated where N_i is the number of animals in the i^{th} dose group, X_i is the number of animals in the i^{th} dose group with a tumor response, P_i is the probability of a response in the i^{th} dose group estimated by fitting the multistage model to the data, and h is the number of remaining groups. The fit is determined to be unacceptable whenever X^2 is larger that the cumulative 99% point of the chi-square distribution with f degrees of freedom, where f equals the number of dose groups minus the number of non-zero multistage coefficients.

Selection of Data--

For some chemicals, a number of studies in different animal species, strains, and sexes, each run at varying doses and routes of exposure, are available. A choice must be made as to which of the data sets is appropriate for use with the model. It may also be necessary to correct for metabolism differences between species and absorption factors via different routes of administration. The following procedures are used by the CAG in evaluating these data; they are consistent with the approach of making a maximum-likely risk estimate.

1. The data on tumor incidence are separated according to organ sites or tumor types. The dose and tumor incidence data set used in the model is the set in which the incidence is statistically significantly higher than in controls for at least one test dose level, and/or where the tumor incidence rate shows a statistically significant trend with respect to dose level. The data set that gives the highest estimate of the lifetime carcinogenic risk, q_1^*, is selected in most cases. However, efforts are made to exclude data sets that produce spuriously high risk estimates because of small numbers of animals. That is, if two sets of data show a similar dose-response relationship, and one has a very small sample size, the data set having the larger sample size is selected for calculating the carcinogenic potency.

2. If there are two or more data sets of comparable size that are identical with respect to species, strain, sex, and tumor sites, the geometric mean of q_1^*, estimated from each of these data sets, is used for risk assessment. The geometric mean of numbers A_1, A_2, ..., A_m is defined as

$$(A_1 \times A_2 \times \ldots \times A_m)^{1/m}$$

3. If two or more significant tumor sites are observed in the same study, and if the data are available, the number of animals with at least one of the specific tumor sites under consideration is used as incidence data in the model.

Calculation of Human Equivalent Dosages from Animal Data--

Following the suggestion of Mantel and Schneiderman (1975), it is assumed that mg/surface area/day is an equivalent dose between species. Since, to a close approximation, the surface area is proportional to the two-thirds power of the weight, as would be the case for a perfect sphere, the exposure in mg/day per two-thirds power of the weight is also considered to be equivalent exposure. In an animal experiment this equivalent dose is computed in the following manner: Let

L_e = duration of experiment

l_e = duration of exposure

m = average dose per day in mg during administration of the agent (i.e., during l_e), and

W = average weight of the experimental animal

Then, the lifetime average exposure is

$$d = \frac{l_e \times m}{L_e \times W^{2/3}}$$

Inhalation--When exposure is via inhalation, the calculation of dose can be considered for two cases where 1) the carcinogenic agent is either a completely water-soluble gas or an aerosol and is absorbed proportionally to the amount of air breathed in, and 2) where the carcinogen is a poorly water-soluble gas which reaches an equilibrium between the air breathed and the body compartments. After equilibrium is reached, the rate of absorption of these agents is expected to be proportional to the metabolic rate, which in turn is proportional to the rate of oxygen consumption, which in turn is a function of surface area.

Case 1--Agents that are in the form of particulate matter or virtually completely absorbed gases, such as sulfur dioxide, can reasonably be expected to be absorbed proportionally to the breathing rate. In this case the exposure in mg/day maybe expressed as

$$m = I \times v \times r$$

where I = inhalation rate per day in m^3, v = mg/m^3 of the agent in air, and r = the absorption fraction.

The inhalation rates, I, for various species can be calculated from the observations of the Federation of American Societies for Experimental Biology (1974) that 25-g mice breathe 34.5 liters/day and 113-g rats breathe 105 liters/day. For mice and rats of other weights, W (in kilograms), the surface area proportionality can be used to find breathing rates in m^3/day as follows:

$$\text{For mice, } I = 0.0345\ (W/0.025)^{2/3}\ m^3/\text{day}$$

$$\text{For rats, } I = 0.105\ (W/0.113)^{2/3}\ m^3/\text{day}$$

For humans, the value of 20 m^3/day is adopted as a standard breathing rate. The equivalent exposure in $mg/W^{2/3}$ for these agents can be derived from the air intake data in a way analogous to the food intake data. The empirical factors for the air intake per kg per day, i = I/W, based upon the previously stated relationships, are tabulated as follows:

Species	W	i = I/W
Man	70	0.29
Rats	0.35	0.64
Mice	0.03	1.3

Therefore, for particulates or completely absorbed gases, the equivalent exposure in $mg/W^{2/3}$ is

$$d = \frac{m}{W^{2/3}} = \frac{Ivr}{W^{2/3}} = \frac{iWvr}{W^{2/3}} = iW^{1/3}vr$$

In the absence of experimental information or a sound theoretical argument to the contrary, the fraction absorbed, r, is assumed to be the same for all species.

Case 2--The dose in mg/day of partially soluble vapors is proportional to the O_2 consumption, which in turn is proportional to $W^{2/3}$ and is also proportional to the solubility of the gas in body fluids, which can be expressed as an absorption coefficient, r, for the gas. Therefore, expressing the O_2 consumption as $O_2 = k\,W^{2/3}$, where k is a constant independent of species, it follows that

$$m = k\,W^{2/3}$$

or

$$d = \frac{m}{W^{2/3}} = kvr$$

As with Case 1, in the absence of experimental information or a sound theoretical argument to the contrary, the absorption fraction, r, is assumed to be the same for all species. Therefore, for these substances a certain concentration in ppm or ug/m^3 in experimental animals is equivalent to the same concentration in humans. This is supported by the observation that the minimum alveolar concentration necessary to produce a given "stage" of anesthesia is similar in man and animals (Dripps et al. 1977). When the animals are exposed via the oral route and human exposure is via inhalation, or vice versa, the assumption is made, unless there is pharmacokinetic evidence to the contrary, that absorption is equal by either exposure route.

Calculation of the Unit Risk from Animal Studies--

The 95% upper-limit risk associated with d mg/$kg^{2/3}$/day is obtained from GLOBAL79 and, for most cases of interest to risk assessment, can be adequately approximated by $P(d) = 1 - \exp(-q_1^* d)$. A "unit risk" in units X is simply the risk corresponding to an exposure of X = 1. This value is estimated by finding the number of mg/$kg^{2/3}$/day that corresponds to one unit of X and substituting this value into the above relationship. Thus, for example, if X is in units of ug/m^3 in the air, we have that for case 1, $d = 0.29 \times 70^{1/3} \times 10^{-3}$ mg/$kg^{2/3}$/day, and for case 2, d = 1, when ug/m^3 is the unit used to compute parameters in animal experiments.

If exposures are given in terms of ppm in air, the following calculation may be used:

$$1 \text{ ppm} = 1.2 \times \frac{\text{molecular weight (gas)}}{\text{molecular weight (air)}} \text{ mg/m}^3$$

Note that an equivalent method of calculating unit risk would be to use mg/kg for the animal exposures and then increase the j^{th} polynomial coefficient by an amount

$$(W_h/W_a)^{j/3} \qquad j = 1, 2, \ldots, k$$

and use mg/kg equivalents for the unit risk values.

Model for Estimation of Unit Risk Based on Human Data

If human epidemiologic studies and sufficiently valid exposure information are available for the compound, they are always used in some way. If they show a carcinogenic effect, the data are analyzed to give an estimate of the linear dependence of cancer rates on lifetime average dose. If they show no carcinogenic effect when positive animal evidence is available, then it is assumed that a risk does exist, but it is smaller than could have been observed in the epidemiologic study, and an upper limit to the cancer incidence is calculated assuming hypothetically that the true incidence is just below the level of detection in the cohort studied, which is determined largely by the cohort size. Whenever possible, human data are used in preference to animal bioassay data.

Very little information exists that can be used to extrapolate from high exposure occupational studies to low environmental levels. However, if a number of simplifying assumptions are made, it is possible to construct a crude dose-response model whose parameters can be estimated using vital statistics, epidemiologic studies, and estimates of worker exposures.

In human studies, the response is measured in terms of the relative risk of the exposed cohort of individuals compared to the control group. The mathematical model employed assumes that for low exposures the lifetime probability of death from lung cancer (or any cancer), P_0, may be represented by the linear equation

$$P_0 = A + B_H x$$

where A is the lifetime probability in the absence of the agent, and x is the average lifetime exposure to environmental levels in units such as ppm. The factor B_H is the increased probability of cancer associated with each unit increase of x, the agent in air.

If it is assumed that R, the relative risk of cancer for exposed workers as compared to the general population, is independent of the length of exposure or age at exposure and depends only on the average lifetime exposure, it follows that

$$R = \frac{P}{P_0} = \frac{A + B_H (x_1 + x_2)}{A + B_H x_1}$$

or

$$RP_0 = A + B_H (x_1 + x_2)$$

where x_1 = lifetime average daily exposure to the agent for the general population, x_2 = lifetime average daily exposure to the agent in the occupational setting, and P_0 = lifetime probability of dying of cancer with no or negligible exposure.

Substituting $P_0 = A + B_H x_1$ and rearranging gives

$$B_H = P_0 (R - 1)/x_2$$

To use this model, estimates of R and x_2 must be obtained from the epidemiologic studies. The value P_0 is derived by means of the life table methodology from the age- and cause-specific death rates for the general population found in the 1978 U.S. Vital Statistics tables.

UNIT RISK ESTIMATES FOR CADMIUM

Unit Risk Estimate Based on an Animal Study

The bioassay by Takenaka et al. (1983) using male Wistar rats and cadmium chloride aerosol was chosen for estimating the quantitative unit risk of cadmium. This was the only positive animal inhalation study with cadmium and/or cadmium compounds that showed a dose-response trend of primary lung carcinomas to animals continuously exposed to cadmium chloride aerosols for 18 months. The primary lung carcinomas were histologically differentiated as adenocarcinomas, epidermoid carcinomas, combined epidermoid and adenocarcinomas, and mucoepidermoid carcinomas, but were combined for this unit risk analysis. The incidences of total primary lung carcinomas was 15% (6/39), 53% (20/38), and 71% (25/35) for the low (12.5 ug/m^3), medium (25 ug/m^3), and high (50 ug/m^3) exposure groups, respectively. No tumors were found among 38 controls.

In arriving at an upper-limit unit risk estimate for humans, dose is calculated on a lifetime continuous basis with 2 years considered a full lifetime exposure for rats. Thus, by multiplying by 0.75 the measured concentrations of 13.4 ug/m^3, 25.7 ug/m^3, and 50.8 ug/m^3 for the three dose groups, the lifetime continuous exposure can be estimated as 10.05 ug/m^3, 19.3 ug/m^3, and 38.1 ug/m^3, respectively. The corrections for animal to human weight differences are given below.

In transforming from animal exposure to human equivalence, the method for treating inhalation of an aerosol (presented earlier in the section for calculation of human equivalent dosages from animal data [Case 1]), assumes aerosols to be absorbed proportionally to the breathing rate. The breathing rate for

113-g rats is 0.105 m^3/day. For the Wistar rats used in the Takenaka et al. bioassay, the average weights at 18 months were 424.6 g (for the 13.4 ug/m^3 group), 437.6 g (for the 25.7 ug/m^3 group), and 424.3 g (for the 50.8 ug/m^3 group). To adjust for these weights the foloowing formula is used:

$$I = 0.105\ (W/0.113)^{2/3}\ m^3/day$$

where I = the daily inhalation rate of a rat weighing W kilograms. For the three groups the I values are 0.254 m^3/day, 0.259 m^3/day, and 0.254 m^3/day, respectively. Combining these with the lifetime continuous exposure estimates above, daily exposure is estimated to be 2.55 ug/day, 5.00 ug/day, and 9.68 ug/day, respectively. Equivalently, dose can be estimated on a ug/kg/day basis as 6.0 ug/kg/day, 11.4 ug/kg/day, and 22.8 ug/kg/day.

Based on the above data for animals, the 95% upper-limit unit risk of cancer resulting from cadmium chloride exposure is $q_1^* = 6.3 \times 10^{-2} (ug/kg/day)^{-1}$ using the linearized multistage model. When transformed to equivalent human dose, the CAG method requires multiplying q_1^* by the weight ratio factor $(W_h/W_a)^{1/3}$, where W_h = weight of a human, which is assumed to be 70 kg. Thus,

$$q_h^* = q_1^*\ (W_h/W_a)^{1/3} = 6.3 \times 10^{-2}(70/0.429)^{1/3} = 3.4 \times 10^{-1}(ug/kg/day)^{-1}$$

Thus, using the linearized multistage model, the 95% upper-limit unit risk estimate for induced cancers based on cadmium chloride exposure is $q_h^* = 3.4 \times 10^{-1}$. If it is assumed that the Cd^{++} ion is the carcinogenic agent and not the cadmium chloride molecule, then an adjustment must be made for the weight of the two chloride ions. In this case the molecular weight contribution of cadmium to the total molecular weight is 112.4/183.3 = 0.613. The interpretation in terms of risk is that a q_h^* for the cadmium ion based on inhalation of cadmium chloride is

$$q_h^* = 3.4 \times 10^{-1}(\text{ug/kg/day})^{-1}/0.613 = 5.5 \times 10^{-1}(\text{ug/kg/day})^{-1}$$

This can be converted back to human exposure in terms of ug/m^3 by assuming that a 70-kg human breathes 20 m^3 air/day. Thus,

$$q_h^* = 3.4 \times 10^{-1}(\text{ug/kg/day})^{-1} \times \frac{1}{70\text{ kg}} \times \frac{20\text{ m}^3}{\text{day}} = 9.7 \times 10^{-2}(\text{ug/m}^3)^{-1}$$

for cadmium chloride exposure, and

$$q_h^* = 9.7 \times 10^{-2}(\text{ug/m}^3)^{-1}/0.613 = 1.6 \times 10^{-1}(\text{ug/m}^3)^{-1}$$

based on inhalation exposure to the cadmium ion. Therefore, the unit risk from the inhalation of one microgram of elemental cadmium per cubic meter of air is approximately

$$R = 1 - \exp -(0.16 \times 1) = 0.15$$

This is an upper-bound estimate of risk based on the direct experimental evidence presently available. Using other dose-response models to estimate risk (as shown in Appendix A) can give considerably lower estimates than those obtained using the upper-bound multistage model. However, there is no direct evidence suggesting that these alternative models provide a more rational basis for estimating risk than the upper-bound multistage model. It must be kept in mind that the alternative models have the potential for seriously underestimating the true risk at low levels of environmental exposure to cadmium.

Unit Risk Estimate Based on a Human Study

Data Base--

At the present time the strongest evidence in humans suggesting a cadmium-induced carcinogenic response is found in the Thun et al. (1984) study. This response was observed in a cohort of cadmium smelter workers who were hired on or after January 1, 1926, and were employed for at least 2 years in a production capacity in the same plant from January 1, 1940, to December 31, 1969. This cohort of white males had a total of 16 respiratory cancer deaths through December 31, 1978, while only 6.99 would be expected based on calendar time age-specific respiratory cancer death rates for U.S. white males. Assuming that the U.S. white male population is a valid control population for the cohort of cadmium smelter workers, the probability of obtaining 16 or more respiratory cancer deaths if there was no effect due to cadmium is only 0.0024, based on the exact Poisson Test.

A number of problems arise in using these data to obtain a quantitative estimate of human respiratory cancer risk due to cadmium exposure. Among them are the following:

1. There is some evidence that the smoking rate for the cadmium workers was higher than that of the general white male population.
2. The exposure to cadmium is confounded with exposure to arsenic, a known respiratory carcinogen.
3. Very limited evidence exists concerning the exposure rate and the duration of exposure for the members of the cohort.
4. No exposure estimates exist for individuals.
5. To obtain an estimate of risk, a mathematical model must be assumed that cannot be evaluated for goodness of fit in any reasonable manner using the available data.

In spite of these considerable shortcomings, the CAG nevertheless feels that a risk estimate based on this limited and potentially biased data base could be of use for the following reasons:

1. The observed human respiratory cancer response corresponded to the animal response in regard to site, which increases the likelihood that the response was real.

2. Most of the factors that are potentially biasing would work to increase the apparent cadmium-induced cancer risk. Thus, such a risk estimate should be considered an upper-bound estimate. If this upper-bound estimate is lower than the one obtained in the animal experiment, it should be used in preference to the animal estimate.

Estimation of the Factors Used in the Calculation of B_H--

As noted, three factors need to be addressed in order to estimate the human slope B_H: P_0, the lifetime background risk due to respiratory cancer for the environmentally exposed population; R, the relative risk in the epidemiologic study; and X, the average lifetime exposure for the cadmium-exposed cohort in the epidemiologic study.

Because of the rather limited information available at the present time, considerable uncertainty surrounds the estimation of these factors. Therefore the most prudent approach seems to be to use this limited information to make an educated guess as to the best estimates of each quantity under consideration. Where appropriate, upper and lower bounds are given for each quantity, giving a range of values that in each case is likely to include the true value. A discussion of each of the terms follows.

Lifetime background respiratory cancer risk in the environmentally exposed population (P_0)--The underlying mathematical model for human slope assumes that the background rate for an environmentally exposed population is increased per unit of lifetime exposure by the same "percentage" as the epidemiologically studied population. At present, there is no indication that the environmentally exposed population differs in sex-race distribution from the general U.S. population. As a result, the value calculated from the 1978 vital statistics for the total U.S. population can be used for the lifetime respiratory cancer background death rate. Using the techniques discussed by Gail (1975) the value, $P_0 = 0.046$, is calculated and used as the best estimate.

Vital statistics for 1978 were used for the above calculation because they are the most current available. However, the most appropriate rate to use would be the future unknown value. Since smoking is the most important factor in determining the risk of respiratory cancer, and the smoking rate for females is beginning to approach that of males, the value calculated for the U.S. male population in 1978 is used as an upper bound for the calculation of P_0. This gives a value of $P_{0u} = 0.068$. The rate based on vital statistics of never-smokers during the 1960s is used as a lower limit. This gives a value for P_{0L} of 0.0082.

True relative risk of respiratory cancer due to cadmium in exposed cohort (R)--The observed number is taken as a best estimate of the expected number of cases in the cadmium exposure group, so that $E_x = 16$. The expected number of cases under the assumption of no cadmium effect is taken as the expected number of cases calculated by Thun et al. (1984) to be 6.99. Thus the CAG's best estimate of relative risk is $R = E_x/E = 16/6.99 = 2.29$.

With regard to the calculation of a lower bound for the relative risk, the following should be noted. Based on a worst-case scenario and an arsenic risk model from the National Institute for Occupational Safety and Health, Thun et al. (1984) calculated that at most the number of expected cases of respiratory cancer due to exposure to arsenic for the cadmium worker cohort was 0.78. Also, based on a retrospective smoking survey of cadmium workers and their surviving relatives, and using the smoking adjustment methods developed by Axelson (1978), Thun et al. (1984) estimated that the increase in the expected number of respiratory cancers in the cadmium-exposed worker population due to excess over standard U.S. smoking rates was less than 25%.

Under the assumption that arsenic is additive to background, and smoking is multiplicative, the upper bound for the expected number of cases, assuming no cadmium effect, is $E_u = (6.99 + 0.78) \times 1.25 = 9.71$.

The 95% lower bound on the expected number of cases in the exposed population where 16 were observed is calculated from the relationship

$$0.95 = \sum_{j=0}^{15} e^{-E_{xL}} E_{xL}^{j}/j!$$

which has the solution $E_{xL} = 10.11$.

Thus the CAG's lower bound estimate for the relative risk is

$$R_L = \frac{E_{xL}}{E_u} = 10.11/9.71 = 1.041$$

To calculate an upper bound for the relative risk, the following approach is taken. The white male respiratory cancer rate is 10-25% lower for Colorado-Denver males than the U.S. rates used in the expected-value calculations. Since Denver is the area where the plant is located, a lower bound on the expected number of cases under the assumption of no cadmium effect is $E_L = 6.99 \times 0.75 = 5.24$. The 95% upper bound for the expected number of cases in the cadmium-exposed population, given that 16 were observed, is calculated from the relationship

$$0.05 = \sum_{j=0}^{16} e^{-E_{xu}} E_{xu}^{j}/j!$$

which has the solution

$$E_{xu} = 23.23$$

Thus the upper bound for the relative risk is

$$R_U = \frac{E_{xu}}{E_L} = 23.23 \div 5.24 = 4.43$$

Lifetime average exposure for members of cadmium cohort (X)--To estimate the average lifetime exposure on a continuous basis, a number of factors need to be estimated. They are:

The average age, t, of the cohort at the end of the observation period.

The average duration, d, of exposure for the cohort in years.

The average exposure rate, e, on the job.

The fraction, f, of time per year exposed on the job.

Given these factors, an estimate of the average exposure rate over the cohort's lifetime is

$$X = def/t$$

A discussion of each of these factors follows.

Average age at end of observation period (t)--No direct information is available concerning the ages of the entire cohort at the end of the observation period. However, the average of the 51 individuals who died of causes thought to be possibly cadmium-related can be used as an upper bound. This results in $t_U = 63.3$ years. In calculating a lower bound, it is noted that 50% of the population had 33 years or more of follow-up. Assuming that an average starting age is 20 years and that the mean and median ages are equal, the result is a lower bound of $t_L = 20 + 33 = 53$ years. For a best estimate, the midpoint of the upper and lower bounds is used to yield an estimate of $t = (63.3 + 53) \div 2 = 58.2$ years.

Average duration of exposure (d)--As noted by Thun et al. (1984), the standard rate ratios (SRRs) were closely related to the standard mortality ratios (SMRs) and virtually uniform over duration of employment. Thus, the expected number of cases is proportional to the observed number of cases. As a first-order approximation it is assumed that person-years of observation are also proportional to the observed number of cases. Table 18 shows the weighted average low, best, and high estimated durations as calculated using this approach.

TABLE 18. ESTIMATED DURATIONS OF EXPOSURE

Duration of employment	Assumed average in interval Low	Best	High	Number of deaths
2-10	2	6	10	9
10-20	10	15	20	3
20+	20	30	40	4
Weighted average(d)	8.00	13.69	19.38	

Average exposure rate on the job (e)--Smith et al. (1980) estimated inhalation exposures that occurred in various work areas, as shown in Table 16. These estimated exposures were time-weighted with approporiate adjustments for the use of respirators.

Since information concerning the distribution of person-years of observation associated with exposures over time and location is not presently available, the best estimate would be the average, giving equal weight to each time period and production department. The resulting estimate is $e = 0.53$ mg/m^3. For an upper bound, the average for the eight plant production departments during the pre-1950 period is calculated as $e_U = 1.04$ mg/m^3. The lower bound is the average for the eight production departments during the 1965 to 1976 time period, or $e_L = 0.26$ mg/m3.

Fraction of the time per year exposed on the job (f)--It is assumed that individuals worked 40 hours per week and were absent 20 days per year due to vacation, holidays, and illness. This results in an estimate of

$$f = \frac{8}{24} \times \frac{240}{365} = 0.22$$

Calculation of Average Lifetime Exposure (X)--

The previous information concerning exposure is summarized in Table 19.

TABLE 19. SUMMARY OF EXPOSURE

Factor	Value maximizing average exposure	Value giving best estimate average exposure	Value minimizing average exposure
t	53.0	58.2	63.3
d	19.4	13.7	8.0
e	1.04	0.53	0.26
f	0.22	0.22	0.22
$X = def/t \times 10^3$ ug/m^3	83.4	27.4	7.2

Calculation of Human Slope (B_H)--

The values needed to calculate the estimated human slope for a constant exposure of 1 ug/m^3 are given in Table 20. The effects of compounding, especially multiplying together, a series of assumptions that consistently overestimates or underestimates the true values of parameters used to estimate risk leads to very different estimates. This is true even when the mathematical model itself, a major source of uncertainty, remains the same. However, it is highly unlikely

TABLE 20. VALUES USED TO ESTIMATE HUMAN SLOPE AND ITS BOUNDS

Factor	Value maximizing slope	Value giving best estimate of slope	Value minimizing slope
P_0	0.068	0.046	0.008
E	5.24	6.99	9.71
E_x	23.23	16	10.11
$R = E_x/E$	4.43	2.29	1.04
X	7.2	27.4	83.4
$B_H = P_0(R-1)/X =$	3.3×10^{-2}	2.0×10^{-3}	3.8×10^{-6}

that either extreme is close to the true value. The CAG takes as its estimate the value obtained by compounding the series of best guesses. Although a single term may not be conservative, the overall result is probably more reasonable than either of the extremes.

One final correction is needed. The assumption is that human exposure was to cadmium oxide (CdO); thus, the risk from elemental cadmium is increased by the ratio

$$(CdO/Cd) = (128.4/112.4) = 1.14$$

with a corresponding unit risk estimate of

$$B_H = 2.0 \times 10^{-3} \times 1.14 = 2.3 \times 10^{-3}\ (ug/m^3)^{-1}$$

This estimate is two orders of magnitude lower than the estimate based on the rat inhalation study of Takenaka et al. (1983), which was 0.156. The range is 4.3 x 10^{-6} to 3.8 x 10^{-2}, so that the upper bound is also smaller than in the rat study cited. Some of this difference might be due to variation in biological activity between cadmium compounds (i.e., cadmium chloride in rats versus cadmium fumes and dust in humans). For example, in the Takenaka et al. (1983) study, it may be that these concentrations tended to inhibit lung clearance by suppression of macrophage activity. In any event, the final unit risk estimate is based on data from the human study (Thun et al. 1984), which is also used for calculating the relative potency of cadmium.

RELATIVE POTENCY

One of the uses of the concept of unit risk is to compare the relative potencies of carcinogens. For the purposes of the present analysis, potency is defined as the linear portion of the dose-response curve, and is used to calculate the required unit risk factors. In this section, the potency of cadmium is compared with that of other chemicals that the CAG has evaluated as suspect carcinogens. To estimate the relative potency on a per mole basis, the unit risk slope factor is multiplied by the molecular weight and the resulting number, expressed in terms of $(\mathrm{mMol/kg/day})^{-1}$, is called the relative potency index.

Figure 2 is a histogram representing the frequency distribution of relative potency indices for 54 chemicals that have been evaluated by the CAG as suspect carcinogens. The actual data summarized by the histogram are presented in Table 21. Where human data have been available for a compound, such data have been used to calculate these indices. Where no human data have been available, data from animal oral studies and animal inhalation studies have been used in that order, since animal oral studies have been conducted for most of these compounds, and the use of such studies provides a more consistent basis for potency comparisons.

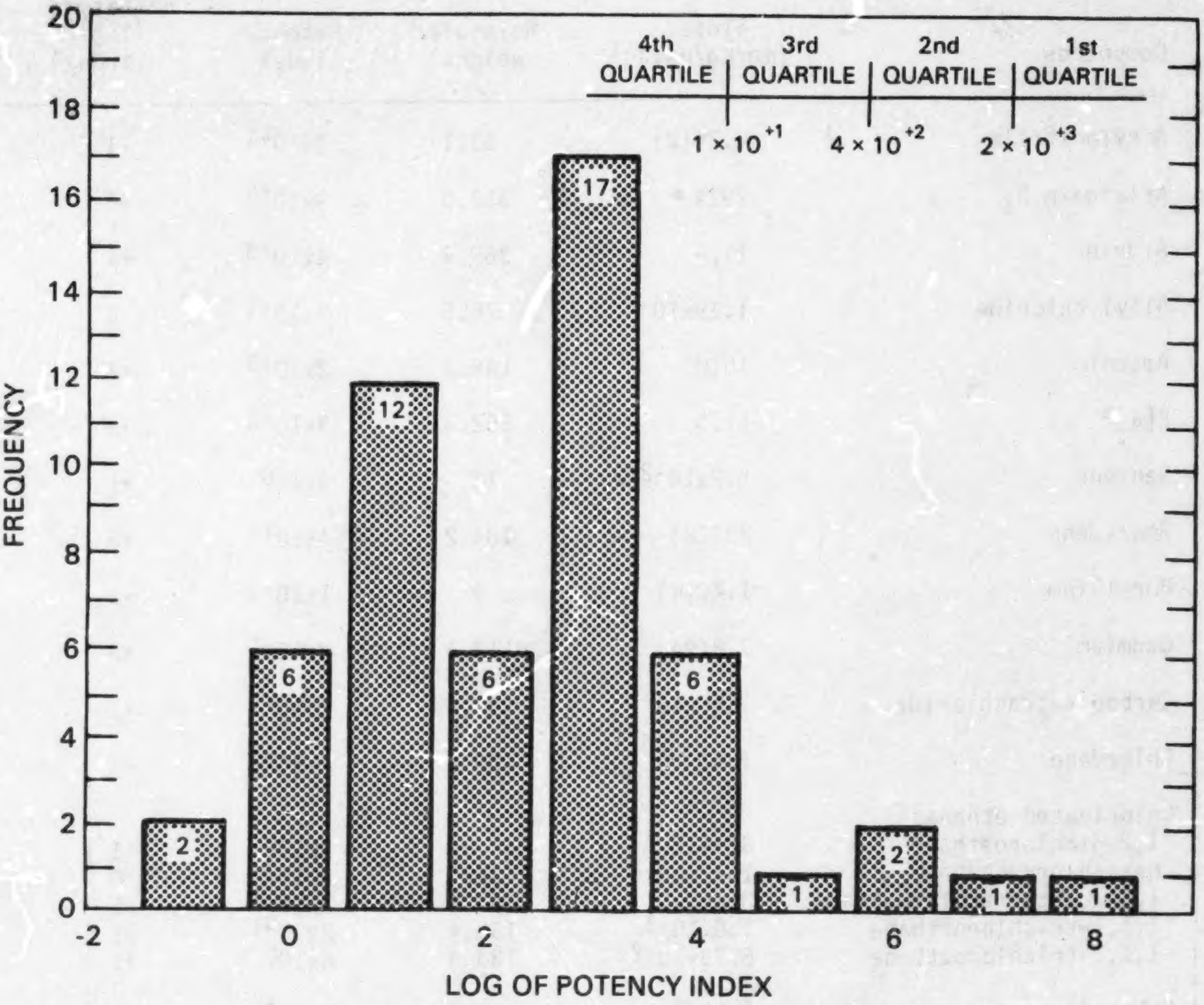

Figure 2. Histogram representing the frequency distribution of the potency indices of 54 suspect carcinogens evaluated by the Carcinogen Assessment Group.

TABLE 21. RELATIVE CARCINOGENIC POTENCIES AMONG 54 CHEMICALS EVALUATED BY THE CARCINOGEN ASSESSMENT GROUP AS SUSPECT HUMAN CARCINOGENS[1,2,3]

Compounds	Slope (mg/kg/day)$^{-1}$	Molecular weight	Potency index	Order of magnitude (log^{10} index)
Acrylonitrile	0.24(W)	53.1	1x10^{+1}	+1
Aflatoxin B$_1$	2924	312.3	9x10^{+5}	+6
Aldrin	11.4	369.4	4x10^{+3}	+4
Allyl chloride	1.19x10^{-2}	76.5	9x10^{-1}	0
Arsenic	15(H)	149.8	2x10^{+3}	+3
B[a]P	11.5	252.3	3x10^{+3}	+3
Benzene	5.2x10^{-2}(W)	78	4x10^{0}	+1
Benzidene	234(W)	184.2	4x10^{+4}	+5
Beryllium	1.40(W)	9	1x10^{+1}	+1
Cadmium	7.8(W)	112.4	9x10^{+2}	+3
Carbon tetrachloride	1.30x10^{-1}	153.8	2x10^{+1}	+1
Chlordane	1.61	409.8	7x10^{+2}	+3
Chlorinated ethanes				
1,2-dichloroethane	6.9x10^{-2}	98.9	7x10^{0}	+1
hexachloroethane	1.42x10^{-2}	236.7	3x10^{0}	0
1,1,2,2-tetrachloroethane	0.20	167.9	3x10^{+1}	+1
1,1,1-trichloroethane	1.6x10^{-3}	133.4	2x10^{-1}	-1
1,1,2-trichloroethane	5.73x10^{-2}	133.4	8x10^{0}	+1
Chloroform	7x10^{-2}	119.4	8x10^{0}	+1
Chromium	41(W)	100	4x10^{+3}	+4
DDT	8.42	354.5	3x10^{+3}	+3
Dichlorobenzidine	1.69	253.1	4x10^{+2}	+3
1,1-dichloroethylene	1.47x10^{-1}(I)	97	1x10^{+1}	+1
Dieldrin	30.4	380.9	1x10^{+4}	+4

(continued on the following page)

TABLE 21. (continued)

Compounds	Slope (mg/kg/day)$_{-1}$	Molecular weight	Potency index	Order of magnitude ($\log_{10}$ index)
Dinitrotoluene	0.31	182	$6x10^{+1}$	+2
Diphenylhydrazine	0.77	180	$1x10^{+2}$	+2
Epichlorohydrin	$9.9x10^{-3}$	92.5	$9x10^{-1}$	0
Bis(2-chloroethyl)ether	1.14	143	$2x10^{+2}$	+2
Bis(chloromethyl)ether	9300(I)	115	$1x10^{+6}$	+6
Ethylene dibromide (EDB)	8.51	187.9	$2x10^{+3}$	+3
Ethylene oxide	1.26(I)	44.1	$6x10^{+1}$	+2
Heptachlor	3.37	373.3	$1x10^{+3}$	+3
Hexachlorobenzene	1.67	284.4	$5x10^{+2}$	+3
Hexachlorobutadiene	$7.75x10^{-2}$	261	$2x10^{+1}$	+1
Hexachlorocyclohexane				
technical grade	4.75	290.9	$1x10^{+3}$	+3
alpha isomer	11.12	290.9	$3x10^{+3}$	+3
beta isomer	1.84	290.9	$5x10^{+2}$	+3
gamma isomer	1.33	290.9	$4x10^{+2}$	+3
Hexachlorodibenzodioxin	$1.1x10^{+4}$	391	$4x10^{+6}$	+7
Methylene chloride	$6.3x10^{-4}$	84.9	$5x10^{-2}$	-1
Nickel	1.15(W)	58.7	$7x10^{+1}$	+2
Nitrosamines				
Dimethylnitrosamine	25.9(not by q_1^*)	74.1	$2x1C^{+3}$	+3
Diethylnitrosamine	43.5(not by q_1^*)	102.1	$4x10^{+3}$	+4
Dibutylnitrosamine	5.43	158.2	$9x10^{+2}$	+3
N-nitrosopyrrolidine	2.13	100.2	$2x10^{+2}$	+2
N-nitroso-N-ethylurea	32.9	117.1	$4x10^{+3}$	+4
N-nitroso-N-methylurea	302.6	103.1	$3x10^{+4}$	+4
N-nitroso-diphenylamine	$4.92x10^{-3}$	198	$1x10^{0}$	0
PCBs	4.34	324	$1x10^{+3}$	+3

(continued on the following page)

TABLE 21. (continued)

Compounds	Slope $(mg/kg/day)_{-1}$	Molecular weight	Potency index	Order of magnitude ($\log_{10}$ index)
Phenols				
2,4,6-trichlorophenol	1.99×10^{-2}	197.4	4×10^{0}	+1
Tetrachlorodibenzo-p-dioxin	$1.56 \times 10^{+5}$	322	$5 \times 10^{+7}$	+8
Tetrachloroethylene	3.5×10^{-2}	165.8	6×10^{0}	+1
Toxaphene	1.13	414	$5 \times 10^{+2}$	+3
Trichloroethylene	1.9×10^{-2}	131.4	2.5×10^{0}	0
Vinyl chloride	1.75×10^{-2}(I)	62.5	1×10^{0}	0

Remarks:

1. Animal slopes are 95% upper-limit slopes based on the linearized multistage model. They are calculated based on animal oral studies, except for those indicated by I (animal inhalation), W (human occupational exposure), and H (human drinking water exposure). Human slopes are point estimates based on the linear non-threshold model.

2. The potency index is a rounded-off slope in $(mMol/kg/day)^{-1}$ and is calculated by multiplying the slopes in $(mg/kg/day)^{-1}$ by molecular weight of the compound.

3. Not all of the carcinogenic potencies presented in this table represent the same degree of certainty. All are subject to change as new evidence becomes available.

The potency index for cadmium based on the Thun et al. (1984) study of cadmium smelter workers is $8.8 \times 10^{+2}$ (mMol/kg/day)$^{-1}$. This is derived as follows: Assuming that an individual breathes 20 m^3 of air per day and weighs 70 kg, the slope estimate from the human study, 2.3×10^{-3} (ug/m^3)$^{-1}$, is first converted to units of (mg/kg/day)$^{-1}$ or

$$2.3 \times 10^{-3}(\text{ug/m}^3)^{-1} \times \frac{1 \text{ day}}{20 \text{ m}^3} \times \frac{1 \text{ ug}}{10^{-3} \text{ mg}} \times 70 \text{ kg} = 7.8 \text{ (mg/kg/day)}^{-1}$$

Multiplying by the molecular weight of 112.4 give a potency index of $8.8 \times 10^{+2}$. Rounding off to the nearest order of magnitude gives a value of 10^{+3}, which is the scale presented on the horizontal axis of Figure 2. The index of $8.8 \times 10^{+2}$ lies in the second quartile of the 54 suspect carcinogens.

Ranking of the relative potency indices is subject to the uncertainty of comparing estimates of potency of different species using studies of different quality. Furthermore, all of the indices are based on estimates of low-dose risk using the linearized multistage extrapolation model fitted to the data at relatively high doses. Thus, relative potencies could be different at high exposures, where non-linearities in the dose-response curve could exist.

APPENDIX A

COMPARISON OF RESULTS BY VARIOUS EXTRAPOLATION MODELS

The estimate of unit risk from animals presented in the body of this document was calculated by use of the linearized multistage model. This nonthreshold model is part of a methodology for estimating a conservative linear slope at low extrapolation doses that is usually consistent with the data at all dose levels in an experiment. The model holds that the most plausible upper limits of risk are those predicted by linear extrapolations to low levels of the dose-response relationship.

Other nonthreshold models that have been used for risk extrapolation are the one-hit, the log-Probit, and the Weibull models. The one-hit model is characterized by a continuous downward curvature, but is linear at low doses. Because of its functional form, the one-hit model can be considered the linear form or first stage of the multistage model. This fact, together with the downward curvature of the one-hit model, means that the model will always yield low-level risk etimates that are at least as large as those obtained with the multistage model. In addition, whenever the data can be fitted adequately to the one-hit model, estimates based on the one-hit model and the multistage model will be comparable.

The log-Probit and the Weibull models, because of their general "S" curvature, are often used for the interpretation of toxicological data in the observable range. The low-dose upward curvatures of these two models usually yield lower low-dose risk estimates than those of the one-hit or multistage models.

The log-Probit model was originally used in biological assay problems such as potency assessments of toxicants and drugs, and is most often used to estimate such values as percentile lethal dose or percentile effective dose. The log-

Probit model was developed along stictly empirical lines, in studies where it was observed that several log dose-response relationships followed the cumulative normal probability distribution function, Φ. In fitting the log-Probit model to cancer bioassay data, assuming an independent background, this relationship becomes

$$P(D;a,b,c) = c + (1-c)\,\Phi\,(a+b\log_{10} D) \quad a,b > 0 \leq c < 1$$

where P is the proportion responding at dose D, c is an estimate of the background rate, a is an estimate of the standardized mean of individual tolerances, and b is an estimate of the log-Probit dose-response slope.

The one-hit model arises from the theory that a single molecule of a carcinogen has a quantifiable probability of transforming a single normal cell into a cancer cell. This model has the probability distribution function

$$P(D;a,b) = 1-\exp-(a+bd) \quad a,b > 0$$

where a and b are the parameter estimates (a = the background or zero dose rate, and b = the linear component or slope of the dose-response model). In considering the added risk over background, incorporation of Abbott's correction leads to

$$P(D;b) = 1-\exp-(bd) \quad b > 0$$

Finally, a model from the theory of carcinogenesis arises from the multihit model applied to multiple target cells. This model, known as the Weibull model, is of the form

$$P(D;b,k) = 1-\exp-(bd^{k}) \quad b,k > 0$$

For the power of dose only, the restriction $k > 0$ has been placed on this model. When $k > 1$, the model yields low-dose estimates of risks that are usually significantly lower than either the multistage or the one-hit models, both of which are linear at low doses. All three of these models--the multistage, the one-hit, and the Weibull--usually project risk estimates that are significantly higher at low exposure levels than those projected by the log-Probit model.

The estimates of added risk for low doses for these models are given in Table A-1 for the cadmium chloride rat inhalation studies by Takenaka et al. (1983). Both maximum likelihood estimates and 95% upper confidence limits are presented. The results show that the maximum likelihood estimates of risk for the log-Probit model are all less than those for the other models, and this difference increases sharply at low doses. The one-hit model yields maximum likelihood estimates slightly higher than those obtained with the multistage model, while those obtained with the Weibull model are somewhat lower.

TABLE A-1. ESTIMATES OF LOW-DOSE RISK TO HUMANS EXPOSED TO CADMIUM CHLORIDE BASED ON MALE WISTAR RATS FROM THE TAKENAKA ET AL. (1983) INHALATION STUDY DERIVED FROM FOUR DIFFERENT MODELS

	Maximum likelihood estimates of additional risks				95% upper confidence limit of additional risks			
Dose (ug/m^3)	Multistage model	One-hit model	Weibull model	Log-Probit model	Multistage model[a]	One-hit model	Weibull model	Log-Probit model
10^{-4}	5.5x10-6	8.1x10-6	1.9x10-7	0	9.7x10-6	1.0x10-5	1.3x10-6	1.2x10-38
10^{-3}	5.5x10-5	8.1x10-5	4.1x10-6	0	9.7x10-5	1.0x10-4	2.6x10-5	8.9x10-25
10^{-2}	5.5x10-4	8.1x10-4	8.8x10-5	2.0x10-15	9.7x10-4	1.0x10-3	3.8x10-4	4.4x10-1
10^{-1}	5.5x10-3	8.1x10-3	1.9x10-3	1.3x10-7	9.7x10-3	1.0x10-2	5.9x10-3	1.5x10-6
1	5.5x10-2	7.8x10-2	3.9x10-2	7.0x10-3	9.2x10-2	9.5x10-2	8.1x10-2	2.3x10-2

[a] $q_h^* = 9.7 \times 10^{-2} (ug/m^3)^{-1}$ for the multistage model; $P(d) = 1 - e^{-q_h^* d}$

APPENDIX B

INTERNATIONAL AGENCY FOR RESEARCH ON CANCER (IARC) CRITERIA FOR EVALUATION OF THE CARCINOGENICITY OF CHEMICALS*

ASSESSMENT OF EVIDENCE FOR CARCINOGENICITY FROM STUDIES IN HUMANS

The degrees of evidence for carcinogenicity from studies in humans are categorized as:

1. Sufficient evidence of carcinogenicity, which indicates that there is a causal relationship between the agent and human cancer.

2. Limited evidence of carcinogenicity, which indicates that a causal interpretation is credible, but that alternative explanations, such as chance, bias, or confounding, could not adequately be excluded.

3. Inadequate evidence, which indicates that one of three conditions prevailed: (a) there were few pertinent data; (b) the available studies, while showing evidence of association, did not exclude chance, bias, or confounding; (c) studies were available which do not show evidence of carcinogenicity.

ASSESSMENT OF EVIDENCE OF CARCINOGENICITY FROM STUDIES IN EXPERIMENTAL ANIMALS

These assessments are classified into four gruops:

1. Sufficient evidence of carcinogenicity, which indicates that there is an increased incidence of malignant tumors: (a) in multiple species or strains; (b) in multiple experiments (preferably with different routes of administration or using different dose levels); or (c) to an unusual degree with regard to incidence, site, type of tumor, or age at onset. Additional evidence may be provided by data on dose-response effects, as well as information from short-term tests or on chemical structure.

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*International Agency for Research on Cancer. 1982. IARC Monographs: Evaluation of the Carcinogenic Risk of Chemicals to Humans, Supplement 4. Lyon, France.

2. Limited evidence of carcinogenicity, which means that the data suggest a carcinogenic effect but are limited because: (a) the studies involve a single species, strain, or experiment; (b) the experiments are restricted by inadequate dosage levels, inadequate duration of exposure to the agent, inadequate period of follow-up, poor survival, too few animals, or inadequate reporting; or (c) the neoplasms produced often occur spontaneously and, in the past, have been difficult to classify as malignant by histological criteria alone (e.g., lung and liver tumors in mice).

3. Inadequate evidence, which indicates that because of major qualitative or quantitative limitations, the studies cannot be interpreted as showing either the presence or absence of a carcinogenic effect; or that within the limits of the tests used, the chemical is not carcinogenic. The number of negative studies is small, since, in general, studies that show no effect are less likely to be published than those suggesting carcinogenicity.

4. No data, indicating that data were not available to the working group.

EVALUATION OF CARCINOGENIC RISK TO HUMANS

At present, no objective criteria exist to interpret data from studies in experimental animals or from short-term tests directly in terms of human risk. Thus, in the absence of sufficient evidence from human studies, evaluation of the carcinogenic risk to humans was based on consideration of both the epidemiologic and the experimental evidence. The breadth of the categories of evidence defined above allows substantial variation within each category. The decisions reached by the IARC Working Group regarding overall risk incorporate these differences, even though the differences cannot always be reflected adequately when placing exposures into particular categories.

The chemical, group of chemicals, industrial processes, or occupational exposures were thus put into one of three groups:

Group 1

The chemical, group of chemicals, industrial process, or occupational exposure is carcinogenic to humans. This category was used only when there was sufficient evidence from epidemiologic studies to support a causal association between the exposure and cancer.

Group 2

The chemical, group of chemicals, industrial process, or occupational exposure is probably carcinogenic to humans. This category includes exposures for which, at one extreme, the evidence of human carcinogenicity is almost sufficient, as well as exposures for which, at the other extreme, it is inadequate. To reflect this range, the category was divided into higher (Group A) and lower (Group B) degrees of evidence. Usually, category 2A is reserved for exposures for which there is at least limited evidence of carcinogenicity to humans. The data from studies in experimental animals play an important role in assigning studies to category 2, and particularly those in Group B; thus, the combination of sufficient evidence in animals and inadequate data in humans usually results in a classification of 2B.

In some cases, the IARC Working Group considered that the known chemical properties of a compound and the results from short-term tests allowed its transfer from Group 3 to 2B or from 2B to 2A.

Group 3

The chemical, group of chemicals, industrial process, or occupational exposure cannot be classified as to its carcinogenicity to humans.

REFERENCES

Adamsson, E. 1979. Long-term sampling of airborne cadmium duct in an alkaline battery factory. Scand. J. Work Environ. Health 5:178.

Amacher, D.E., and S.C. Paillet. 1980. Induction of trifluorothymidine-resistant mutants by metal ions in L5178Y/TK$^{+/-}$ cells. Mutat. Res. 78:279-288.

Ames, B.N., W.E. Durston, E. Yamasaki, and F.D. Lee. 1973. Carcinogens are mutagens: A simple test system combining liver homogenates for activation and bacteria for detection. Proc. Natl. Acad. Sci. (USA) 70: 2281-2285.

Ames, B.N., J. McCann, and E. Yamasaki. 1975. Methods for detecting carcinogens and mutagens with the Salmonella/mammalian microsome mutagenicity test. Mutat. Res. 31:347-364.

Andersson, K., C.G. Elinder, C. Hogstedt, and T. Kjellstrom. 1982. Mortality among cadmium workers in a Swedish battery factory. Translated from the article in Swedish entitled "Mortality in battery workers exposed to cadmium and nickel." Report to the Swedish Work Environment Fund.

Armitage, P., and R. Doll. 1954. The age distribution of cancer and a multistage theory of carcinogenesis. Br. J. Cancer 8:1-12.

Armstrong, B.G., and G. Kazantzis. 1983. The mortality of cadmium workers. Lancet, June 25, 1983:1425-1427.

Armstrong, B.G., and G. Kazantzis. 1982 (April). A mortality study of cadmium workers in England: Report to the International Lead Zinc Research Organization. TVC Centenary Institute of Occupational Health, London School of Hygiene and Tropical Medicine, London, England.

Avanzi, M. 1950. Osservazioni sull'attivita citologica di alcuni composti chimici. Caryologia 3:234-248.

Axelson, O. 1978. Aspects on confounding in occupational health epidemiology. Scand. J. Work Environ. Health 4:85-89.

Baader, E.W. 1951. Dtsch. Med. Wochenschr. 484.

Bauchinger, M., E. Schmid, H.J. Einbrodt, and J. Dresp. 1976. Chromosome aberrations in lymphocytes after occupational exposure to lead and cadmium. Mutat. Res. 49:57-62.

Bui, T.H., J. Lindsten, and G.J. Nordberg. 1975. Chromosome analysis of lymphocytes from cadmium workers and Itai-Itai patients. Environ. Res. 9:187-195.

Casto, B. 1976. Letter to Richard Troast, EPA, enclosing mutagenicity data on cadmium chloride and cadmium acetate.

Chandler J.A., B.G. Timms, M.S. Morton, and G.V. Groom. 1976. Proceedings: Effect of cadmium administration in vivo in plasma testosterone and the ultrastructure of accessory sex organs of the rat. J. Endocrinol. 69(3):21.

Chellman, G.J., and C.L. Diamond. 1984. Use of a modified 109-cadmium-hemoglobin assay for quantitation of metallothionein in biological tissues. Toxicologist 4:130.

Chiang, C.L. 1961. Vital statistics. Special Report No. 47. U.S. Department of Commerce, Division of Vital Statistics, Washington, DC, p. 275.

Clive, D., G. Hajian, and M.M. Moore. 1981. Letter to the Editor. Mutat. Res. 89:241-244.

Cox, C.R. 1972. Regression models and life tables. J. Roy. Stat. Soc. B 34:187-220.

Crump, K.S., and W.W. Watson. 1979. GLOBAL79: A Fortran program to extrapolate dichotomous animal carcinogenicity data to low doses. Natl. Inst. Environ. Health Sciences, Contract No. 1-ES-2123.

Crump, K.S., H.A. Guess, and L.L. Deal. 1977. Confidence intervals and test of hypotheses concerning dose-response relations inferred from animal carcinogenicity data. Biometrics 33:437-451.

Deaven, L.L., and E.W. Campbell. 1980. Factors affecting the induction of chromosomal aberrations by cadmium in Chinese hamsters cells. Cytogenet. Cell Genet. 26:251-260.

Degraeve, N. 1971. Modification des effets du methane sulfonate d'ethyl au niveau chromosomique. I. Lesions metalliques. Rev. Cytol. Biol. Veget. 34:233-244.

Degraeve, N. 1981. Carcinogenic, teratogenic, and mutagenic effects of cadmium. Mutat. Res. 86:115-135.

Dekundt, G., and G.B. Gerber. 1979. Chromosomal aberrations in bone marrow cells of mice given a normal or a calcium-deficient diet supplemented with various heavy metals. Mutat. Res. 68:163-168.

Dekundt, G., and M. Deminatti. 1978. Chromosome studies in human lymphocytes after in vitro exposure to metal salts. Toxicology 10:67-75.

Dekundt, G., and A. Leonard. 1975. Cytogenic investigations on leukocytes of workers from a cadmium plant. Environ. Physiol. Biochem. 5:319-327.

Dekundt, G., A. Leonard, and B. Ivanov. 1973. Chromosome aberrations in male workers occupationally exposed to lead. Environ. Physiol. Biochem. 3:132-138.

Dixon, R.L., I.P. Lee, and R.J. Sherins. 1976. Methods to assess reproductive effects of environmental chemicals: Studies of cadmium and boron administered orally. Environ. Health Perspect. 13:59-67.

Dripps, R.D., J.E. Eckenhoff, and L.D. Vandam. 1977. Introduction to anethesia: The principles of safe practice. 5th ed. Philadelphia, PA: W.B. Saunders Company, pp. 121-123.

Ellman, G.L. 1959. Tissue sulfhydryl groups. Arch. Biochem. Biophys. 82:70.

Epstein, S.S., E. Arnold, J. Andrea, W. Bass, and Y. Bishop. 1972. Detection of chemical mutagens by the dominant lethal assay in the mouse. Toxicol. Appl. Pharmacol. 23:288-325.

Favino, A., A. Cavalleri, G. Nazari, and M. Tilli. 1968. Testosterone excretion in cadmium chloride-induced tumours in rats. Med. Lav. 59:36-40.

Federation of American Societies for Experimental Biology (FASEB). 1974. Biological data books. 2nd ed., Vol. 3. (Philip L. Altman and Dorothy S. Dittmen, eds.). Bethesda, MD. Library of Congress No. 72-87738.

Ferreira, N.R., and A. Buoniconti. 1968. Trisomy after colchicine therapy. Lancet 2:1304.

Fraumeni, J.F. 1975. Persons at high risk of cancer. New York, NY: Academic Press.

Friberg, L., and E. Odeblad. 1957. Localization of Cd^{115} in different organs. An autoradiographic study. Acta Pathol. Microbiol. Scand. 41:96.

Friedman, M.A., and J. Staub. 1976. Inhibition of mouse testicular DNA synthesis by mutagens and carcinogens as a potential simple mammalian assay for mutagenesis. Mutat. Res. 37:67-76.

Furst, A., and D. Cassetta. 1972. Failure of zinc to negate cadmium carcinogenesis. Proc. Am. Assoc. Cancer Res. 13:62.

Furst, A., D.M. Cassetta, and D.P. Sasmore. 1973. Proc. West. Pharmacol. 16:150-153.

Gail, M. 1975. Measuring the benefit of reduced exposure to environmental carcinogens. J. Chronic Dis. 28:135-147.

Gasiorek, K., and M. Bauchinger. 1981. Chromosome changes in human lymphocytes after separate and combined treatment with divalent salts of lead, cadmium, and zinc. Environ. Mutagen. 3:513-518.

Ghafghazi, T., and J.H. Mennear. 1973. Effects of acute and subacute cadmium administration on carbohydrate metabolism in mice. Toxicol. Appl. Pharmacol. 26:231-240.

Gilliavod, N., and A. Leonard. 1975. Mutagenicity tests with cadmium in the mouse. Toxicology 5:43-47.

Goldsmith, D.F., A.H. Smith, and A.J. McMichael. 1980. A case-control study of prostate cancer within a cohort of rubber and tire workers. J. Occup. Med. 22(8):533-541.

Grasso, P., and L. Goldberg. 1966. Subcutaneous sarcomas as an index of carcinogenic potency. Food Cosmet. Toxicol. 4:297-312.

Greenspan, B.J., and P.E. Morrow. 1984. The effects of in vitro and aerosol exposure to cadmium as phagocytosis by rat pulmonary macrophages. Fund. Appl. Toxicol. 4:48-57.

Gunn, S.A., T.C. Gould, and W.A.D. Anderson. 1963. Cadmium-induced interstitial cell tumors in rats and mice and their prevention by zinc. J. Natl. Cancer Inst. 31:745-759.

Gunn, S.A., T.C. Gould, and W.A.D. Anderson. 1964. Effect of zinc on carcinogenesis by cadmium. Proc. Soc. Exp. Biol. Med. 115:653-657.

Gunn, S.A., T.C. Gould, and W.A.D. Anderson. 1967. Specific response of mesenchymal tissue to carcinogenesis by cadmium. Arch. Path. 83:493-499.

Haddow, A., et al. 1961. Carcinogenicity of iron preparations and metal-carbonate complexes. Rep. Br. Emp. Cancer Campaign 39:74.

Haddow, A., F.J.C. Roe, C.E. Dukes, and B.C.V. Mitchley. 1964. Cadmium neoplasia: Sarcomata at the site of injection of cadmium sulfate in rats and mice. Br. J. Cancer 18:667-673.

Hadley, J.G., A.W. Conklin, and C.L. Sanders. 1980. Rapid solubilization and translocation of ^{109}CdO following pulmonary deposition. Toxicol. Appl. Pharmacol. 54:156-160.

Hadley, J.G., A.W. Conklin, and C.L. Sanders. 1979. Toxicol. Letters 4:107-111.

Heath, J.C. 1962. Cadmium as a carcinogen. Nature 193:592.

Heath, J.C., and M.R. Daniel. 1964. The production of malignant tumors by cadmium in the rat. Br. J. Cancer 18:124.

Heddle, J.A., and W.R. Bruce. 1977. Comparison of tests for mutagenicity or carcinogenicity using assays for sperm abnormalities, formation of micronuclei, and mutations in Salmonella. In: Origins of human cancer (H.H. Hiatt, J.D. Watson, and J.A. Winsten, eds.). Cold Spring Harbor Conferences on Cell Proliferation. Cold Spring Harbor Laboratory, Cold Spring Harbor, NY.

Hedenstedt, A., U. Rannug, C. Ramel, and V. Wachtmeister. 1979. Mutagenicity and metabolism studies on 12 thiuram and dithiocarbamate compounds used as accelerators in the Swedish rubber industry. Mutat. Res. 68:313-325.

Heering, H., G. Oberdoerster, D. Hochrainer, and H.P. Baumert. 1979. Learning behavior and memory of chronically cadmium exposed rats and organ distribution of cadmium. Commission of the European Communities, Brussels, Doc XII/ENV/64/79, pp. 61-62.

Hernberg, S. 1977. Cadmium. In: Origins of human cancer, Book A: Incidence of cancer in humans (H.H. Hiatt, J.D. Watson, and J.A. Winsten, eds.). Cold Spring Harbor Conferences on Cell Proliferation. Cold Spring Harbor Laboratory, Cold Spring Harbor, NY.

Hirayama, T. 1977. Changing patterns of cancer in Japan, with special reference to the decrease in stomach cancer mortality. In: Origins of human cancer, Book A: Incidence of cancer in humans (H.H. Hiatt, J.D. Watson, and J.A. Winsten, eds.). Cold Spring Harbor Conferences on Cell Proliferation. Cold Spring Harbor Laboratory, Cold Spring Harbor, NY.

Hoffman, D.J., and S.K. Niyogi. 1977. Metal mutagens and carcinogens affect RNA synthesis rates in a distinct manner. Science 198:513-514.

Holden, H. 1969. Cadmium toxicology. Lancet 2:57.

Holden, H. 1980. Further mortality studies on workers exposed to cadmium fumes. Presented at Seminar on Occupational Exposure to Cadmium, March 20, 1980, London, England.

Hsie, A.W., J.P. O'Neil, J.R.S. Sabastian, D.B. Couch, et al. 1978. Quantitative mammalian cell genetic toxicology. In: Application of short-term bioassays in the fractionation and analysis of complex environmental mixtures (Michael D. Waters, Stephen Nesnow, Joellen L. Huisingh, Shahbey Sandhu, and Larry Claxton, eds.). EPA-600/9-78-027. U.S. Environmental Protection Agency, Health Effects Research Laboratory, Environmental Toxicology Division, Research Triangle Park, NC, pp. 293-315.

Humperdinck, K. 1968. Kadmium und lungenkrebs. Med. Klin. 63:948.

Inoue, Y., and T.K. Watanabe. 1978. Toxicity and mutagenicity of cadmium and furylfuramide in Drosophila melanogaster. Jpn. J. Genet. 53:183-189.

Inskip, H., and V. Beral. 1982. Mortality of Shipham residents: 40-year follow-up. Lancet, April 17, 1982:896-899.

International Agency for Research on Cancer (IARC). 1973. Cadmium and inorganic cadmium compounds. Monographs on the evaluation of carcinogenic risk of chemicals to man 2:74. Lyon, France.

International Agency for Research on Cancer (IARC). 1976. Cadmium and the cadmium compounds. Monographs on the evaluation of carcinogenic risk of chemicals to man 11:3974. Lyon, France.

International Agency for Research on Cancer (IARC). 1982. IARC criteria for evaluation of the carcinogenicity of chemicals. Monographs on the evaluation of carcinogenic risk of chemicals to man: Supplement 4. Lyon, France.

Japan Public Health Association. 1979. Epidemiological research on the causes of death in cadmium polluted areas. Japan Public Health Association, Tokyo, Japan. (In Japanese).

Kada, T., K. Tutikawa, and Y. Sodaie. 1972. In vitro and host-mediated assay "rec-assay" procedures for screening chemical mutagens and phloxine, a mutagenic red dye detected. Mutat. Res. 16:165-174.

Kahn, H.A. 1966. The Dorn study of smoking and mortality among U.S. veterans: Report on 8 1/2 years of observation. In: Epidemiological approaches to the study of cancer and other chronic diseases. Monograph No. 19. National Cancer Institute, Bethesda, MD, pp. 1-125.

Kalinina, L.M., and G.N. Polukhina. 1977. Mutagenic effects of heavy metal salts on Salmonella in activation systems in vivo and in vitro. Mutat. Res. 46:223-224. (Abstract).

Kanematsu, N., M. Hara, and T. Kada. 1980. Rec-assay and mutagenicity studies on metal compounds. Mutat. Res. 77:109-116.

Kazantzis, G. 1963. Induction of sarcoma in the rat by cadmium sulfide pigment. Nature 198:1213.

Kazantzis, G., and W.J. Hanbury. 1966. The induction of sarcoma in the rat by cadmium sulfide and cadmium oxide. Br. J. Cancer 20:190.

Kipling, M.D., and J.A.H. Waterhouse. 1967. Cadmium and prostatic carcinoma. Lancet 1:730.

Kjellstrom, T. 1982. Mortality and cancer morbidity in people exposed to cadmium. Report prepared for Health Effects Research Laboratory, U.S. Environmental Protection Agency, Research Triangle Park, N.C. Grant No. R806036101.

Kjellstrom, T., L. Friberg, and B. Rahnster. 1979. Mortality and cancer morbidity among cadmium-exposed workers. Environ. Health Perspect. 28:199-204.

Kneale, G.W., T.F. Mancuso, and A.M. Steward. 1981. A cohort study of the cancer risks from radiation to workers at Hanford. Br. J. Ind. Med. 38:156-166.

Knorre, K. 1970. Ortliche Hautschadigungen an der Albinoratte in der Latenzperiode der Sarkomentwicklung nach Kadmiumchloridinjection. Zentralbl. Allg. Pathol. 113:192-197.

Knorre, D. 1971. Zur Induktion von Hodenzwischenzelltumoren an der Albinoratte durche Kadmiumchlorid. Arch. Geschwulstforsch. 38:257-263.

Kolonel, L.N. 1976. Association of cadmium with renal cancer. Cancer 37:1782-1787.

Kumaraswamy, K.R., and M.R. Rajasekarasetty. 1977. Preliminary studies on the effects of cadmium chloride on the meiotic chromosomes. Curr. Science 46:475-478.

Lee, I., and R. Dixon. 1973. Effects of cadmium on spermatogenesis studied by velocity sedimentation cell separation serial mating. J. Pharmacol. Exp. Ther. 187:641-652.

Lemen, R.A., J.S. Lee., J.K. Wagoner, and H.P. Blejer. 1976. Cancer mortality among cadmium production workers. Ann. N.Y. Acad. Sci. 271:273.

Levan, A. 1945. Cytological reactions induced by inorganic salt solutions. Nature 156:751-752.

Levy, L.S., and J. Clack. 1975. Further studies on the effect of cadmium on the prostate gland. I. Absence of prostatic changes in rats given oral cadmium sulfate for two years. Ann. Occup. Hyg. 17:205-211.

Levy, L.S., J. Clack, and F.J.C. Roe. 1975. Further studies on the effect of cadmium on the prostate gland. II. Absence of prostatic changes in mice given oral cadmium sulfate for eighteen months. Ann. Occup. Hyg. 17:213.

Levy, L.S., F.J.C. Roe, D. Malcolm, G. Kazantzis, J. Clack, and H.S. Platt. 1973. Absence of prostatic changes in rats exposed to cadmium. Ann. Occup. Hyg. 16:111-118.

Loser, E. 1980. A two year oral carcinogenicity study with cadmium on rats. Cancer Letters 9:191.

Lucis, O.J., R. Lucis, and K. Aterman. 1972. Tumorigenesis by cadmium. Oncology 26:53-67.

Mailhes, J.B. 1983. Methyl mercury effects on Syrian hamster metaphase II oocyte chromosomes. Environ. Mutagen. 5:679-686.

Malcolm, D. 1972. Potential carcinogenic effect of cadmium in animals and man. Ann. Occup. Hyg. 15:33.

Mandel, R., and H.J.P. Ryser. 1981. The mutagenic effect of cadmium in bacteria and its synergism with alkylating agents. Abstracts of the Environmental Mutagen Society's Twelfth Annual Meeting, p. 89.

Mantel, N., and M.A. Schneiderman. 1975. Estimating "safe" levels, a hazardous undertaking. Cancer Res. 35:1379-1386.

McMichael, A.J., D.A. Andjelkovic, and H.A. Tyroler. 1976a. Cancer mortality among rubber workers: An epidemiologic study. Ann. N.Y. Acad. Sci. 271:124.

McMichael, A.J., R. Spirtas, J.F. Gamble, and P.M. Tousey. 1976b. Mortality among rubber workers: Relationship to specific jobs. J. Occup. Med. 18(3):178-185.

Milvy, P., and K. Kay. 1978. Mutagenicity of 19 major graphic arts and printing dyes. J. Toxicol. Environ. Health 4:31-36.

Mitra, R., and I. Bernstein. 1977. Nature of the repair process associated with the recovery of E. coli after exposure to Cd^{2+}. Biochem. Biophys. Res. Commun. 74:1450-1455.

Mitra, R., and I. Bernstein. 1978. Single-strand breakage in DNA of E. coli exposed to Cd^{2+}. J. Bacteriol. 133:75-80.

Monson, R.R., and L.J. Fine. 1978. Cancer mortality and morbidity among rubber workers. J. Natl. Cancer Inst. 61(4):1047-1053.

Nishioka, H. 1975. Mutagenic activities of metal compounds in bacteria. Mutat. Res. 311:185-189.

Nogawa, K., et al. 1978. Statistical observations of the dose-response relationships of cadmium based on epidemiological studies in the Kakehashi River basin. Environ. Res. 15:185.

Nogawa, K., S. Kawano, and M. Nishi. 1981. Mortality study of inhabitants in a cadmium-polluted area, with special reference to low molecular weight proteinuria. In: Proceedings of the Third Cadmium Conference, Miami, FL.

Oberdoerster, G., H.P. Baumert, D. Hochrainer, and W. Stoeber. 1979. The clearance of cadmium aerosols after inhalation exposure. Am. Ind. Hygiene Assoc. J. 40:443-450.

Oberdoerster, G., H. Oldiges, and B. Zimmermann. 1980. Lung deposition and clearance of cadmium in rats exposed by inhalation or by intratracheal instillation. Zbl. Bakt. I Abt. Orig. B 170:35-43.

Oberly, T.J., C.E. Piper, and D.S. McDonald. 1982. Mutagenicity of metal salts in the L5178 Y mouse lymphoma assay. J. Toxicol. Environ. Health 9:367-376.

Ochi, T., and M. Ohsawa. 1983. Induction of 6-thioguanine-resistant mutants and single-strand scission DNA by cadmium chloride in cultured Chinese hamster cells. Mutat. Res. 111:69-78.

Oehlkers, F. 1953. Chromosome breaks influenced by chemicals. Heredity Suppl. 6:95-105.

O'Riordan, M.L., E.G. Hughes, and H.J. Evans. 1978. Chromosomal studies on blood lymphocytes of men occupationally exposed to cadmium. Mutat. Res. 58:305-311.

Paton, G.R., and A.C. Allison. 1972. Chromosome damage in human cell culture induced by metal salts. Mutat. Res. 16:332.

Poirier, L.A., K.S. Kasprzak, K.L. Hoover, and M.L. Wenk. 1983. Effects of calcium and magnesium acetates on the carcinogenicity of cadmium chloride in Wistar rats. Cancer Res. 43:4575-4581.

Polukhina, G.N., L.M. Kalinina, and L.I. Lukasheva. 1977. A test system for the detection of the mutagenic activity of environmental pollutants. II. Detection of mutagenic effect of heavy metal salts using in vitro assay with metabolic activation. Genetika 13:1492-1494.

Potts, C.L. 1965. Cadmium proteinuria: The health of battery workers exposed to cadmium oxide dust. Ann. Occup. Hyg. 8:55-61.

Putrament, A.H., H. Baranowska, A. Ejchart, and W. Jachymczyk. 1977. Manganese mutagenesis in yeast. VI. Mn^{2+} uptake, mitochondrial DNA replication and E^R induction, comparison with other divalent cations. Mol. Gen. Genet. 151:69-76.

Ramaiya, L.K., and M.D. Pomerantseva. 1977. Investigation of cadmium mutagenic effect on germ cells of male mice. Genetika 13:59-63.

Ramel, C., and M. Friberg. 1974. Carcinogenic and genetic effects. In: Cadmium in the environment (M. Friberg et al., eds.). Cleveland, OH: CRC Press, p. 133.

Ramel, C., and J. Magnusson. 1979. Chemical induction of nondisjunction in Drosophila. Environ. Health Perspect. 31:59-66.

Reddy, J., D. Svoboda, D. Azarnoff, and R. Dawas. 1973. Cadmium-induced Leydig cell tumors of rat testis: Morphological and cytochemical study. J. Natl. Cancer Inst. 51:891-903.

Roe, F.J.C., C.E. Dukes, K.M. Cameron, R.C.B. Pugh, and B.C.V. Mitchley. 1964. Cadmium neoplasia: Testicular atrophy and Leydig cell hyperplasia and neoplasia in rats and mice following the subcutaneous injection of cadmium salts. Br. J. Cancer 18:674-681.

Rohr, G., and M. Bauchinger. 1976. Chromosome analysis in cell cultures of the Chinese hamster after application of cadmium sulfate. Mutat. Res. 40:125.

Ruposhev, A., and K. Garina. 1977. Modification of mutagenic effects of ethyleneimine by cadmium in Crepis capillaris. Genetika 13:32-36.

Russell, L.B., and B.E. Matter. 1980. Whole mammal mutagenicity tests. Evaluation of five methods. Mutat. Res. 75:279-302.

Sabalina, L.P. 1968. Industrial hygiene in the production and use of cadmium stearate. Hyg. Sanit. (U.S.S.R.) 33(7/9):187-191.

Sanders, C.L., and J.A. Mahaffey. 1984. Carcinogenicity of single and multiple intratracheal instillations of cadmium oxide in the rat. Environ. Res. 33:227-233.

Schmauz, R., and P. Cole. 1974. Epidemiology of cancer of the renal pelvis and ureter. J. Natl. Cancer Inst. 52(5):1431-1434.

Schroeder, H.A., J.J. Balassa, and W.H. Vinton, Jr. 1964. Chromium, lead, cadmium, nickel, and titanium in mice: Effect on mortality, tumors and tissue levels. J. Nutr. 83:239-250.

Schroeder, H.A., J.J. Balassa, and W.H. Vinton, Jr. 1965. Chromium, cadmium, and lead in rats: Effects on life span, tumors, and tissue levels. J. Nutr. 86:51-66.

Scott, R., and E. Aughey. 1979. Methylcholanthrene and cadmium-induced changes in rat prostate. Br. J. Urol. 50:25.

Shankaranarayanan, K. 1967. The effects of nitrogen and oxygen treatments on the frequency of X-ray induced dominant lethals and on the physiology of the sperm in _Drosophila melanogaster_. Mutat. Res. 4:641-661.

Shigematsu, I., S. Kitamura, and J. Takeuchi. 1981. A retrospective mortality study on cadmium-polluted population in Japan. In: Proceedings of Third Cadmium Conference, Miami, FL.

Shimada, T., T. Watanabe, and A. Endo. 1976. Potential mutagenicity of cadmium in mammalian oocytes. Mutat. Res. 40:389-396.

Shiraishi, Y. 1975. Cytogenetic studies in 12 patients with Itai-Itai disease. Humanogenetik 27:31-44.

Shiraishi, Y., and T.H. Yoshida. 1972. Chromosomal abnormalities in cultured leucocyte cells from Itai-Itai disease patients. Proc. Jap. Acad. 48:248-251.

Shiraishi, Y., H. Kurahashi, and T.H. Yoshida. 1972. Chromosomal aberrations in cultured human leucocytes induced by cadmium sulfide. Proc. Jap. Acad. 48:133-137.

Sirover, M.A., and L.A. Loeb. 1976. Infidelity of DNA synthesis _in vitro_: Screening for potential metal mutagens or carcinogens. Science 194:1434-1436.

Smith, T.J., R.J. Anderson, and J.C. Reading. 1980. Chronic cadmium exposures associated with kidney function effects. Am. J. Ind. Med. 1:319-337.

Sorahan, T. 1981. A mortality study of nickel-cadmium battery workers. Cancer Epidemiology Research Unit, University of Birmingham, Birmingham, England.

Sorahan, T., and J.A.H. Waterhouse. 1983. Mortality study of nickel-cadmium battery workers by the method of regression models in life tables. Br. J. Ind. Med. 40:293-300.

Sorsa, M., and S. Pfeifer. 1973. Effects of cadmium on development time and prepupal puffing patterns in _Drosophila melanogaster_. Hereditas 71:273-277.

Sunderman, F.W., Jr. 1977. Cadmium. In: R.A. Goyer and M.A. Mehlman, eds. Advances in modern toxicology, Vol. 2. New York, NY: John Wiley and Sons.

Suter, K.E. 1975. Studies on the dominant-lethal and fertility effects of the heavy metal compounds methylmercuric hydroxide, mercuric chloride, and cadmium chloride in male and female mice. Mutat. Res. 30:365-374.

Sutou, S., K. Yamamoto, H. Sendota, K. Tomomatsu, Y. Shimizu, and M. Sugiyama. 1980a. Toxicity, fertility, teratogenicity, and dominant lethal tests in rats administered cadmium subchronically. I. Toxicity studies. Ecotoxicol. Environ. Safety 4:39-50.

Sutou, S., K. Yamamoto, H. Sendota, and M. Sugiyama. 1980b. Toxicity, fertility, teratogenicity, and dominant lethal tests in rats administered cadmium subchronically. II. Fertility, teratogenicity, and dominant lethal tests. Ecotoxicol. Environ. Safety 4:51-56.

Takahashi, T. 1972. Abnormal mitosis by some mutagens in S. cerevisiae. Bull. Brewery Sci. 18:37-48.

Takenaka, S., H. Oldiges, H. Konig, D. Hochrainer, and G. Oberdoerster. 1983. Carcinogenicity of cadmium aerosols in Wistar rats. J. Natl. Cancer Inst. 70:367-373.

Tarkowski, A.K. 1966. An air-drying method for chromosome preparations from mouse eggs. Cytogenetics 5:394-400.

Theiss, J.C. 1982. Utility of injection site tumorigenicity in assessing the carcinogenic risk of chemicals to man. Reg. Toxicol. Pharmacol. 2:213-222.

Thomas, J.F.A. 1980 (Dec.). Soil contamination at Shipham: Report on studies completed in the village and advice to residents (Shipham Survey Committee). Department of the Environment, London, England.

Thun, M. J., T.M. Schnorr, A.B. Smith, and W.E. Halperin. 1984. Mortality among a cohort of U.S. cadmium production workers: An update. National Institute for Occupational Safety & Health, Washington, DC. (Unpublished).

Tomatis, L. 1977. The value of long-term testing for the implementation of primary prevention in organs of human cancer. In: Origins of human cancer (H.H. Hiatt, J.D. Watson, and J.A. Winsten, eds.). Cold Spring Harbor Conferences on Cell Proliferation. Cold Spring Harbor Laboratory, Cold Spring Harbor, NY, pp. 1339-1357.

Umeda, M., and M. Nishimura. 1979. Inducibility of chromosomal aberrations by metal compounds in cultured mammalian cells. Mutat. Res. 67:221-229.

U.S. Environmental Protection Agency. 1977. The Carcinogen Assessment Group's assessment of cadmium. Washington, DC. (Unpublished).

U.S. Environmental Protection Agency. 1981 (May). Health assessment document for Cadmium. EPA 600/8-81-023 (NTIS PB82-115163). Office of Health and Environmental Assessment, Washington, DC.

U.S. Food and Drug Administration. 1977. Total diet studies (7320.08). Compliance Program Evaluation, Bureau of Foods, Washington, DC.

U.S. Occupational Safety and Health Administration (OSHA). 1983 (Aug. 24). Occupational exposure to inorganic arsenic: Comments of ASARCO, Inc. Federal Register 48:1864-1903.

Van Rosen, G. 1953. Radiomimetic activity and the periodical system of the element. Bot. Notis. 140-141.

Van Rosen, G. 1954. Breaking of chromosomes by the action of elements of the periodical system and some other participants. Hereditas 40:258-263.

Varner, M.O. 1983 (April). Updated epidemiologic study of cadmium smelter workers. Presented at the Fourth International Cadmium Conference. (Unpublished).

Vasudev, V., and N.B. Krishnamurthy. 1979. Dominant lethals induced by cadmium in Drosophila melanogaster. Curr. Science 48:1007-1008.

Venitt, S., and L. Levy. 1974. Mutagenicity of chromates in bacteria and its relevance to chromate carcinogenesis. Nature 250:493-495.

Watanabe, T., and A. Endo. 1982. Chromosome analysis of preimplantation embryos after cadmium treatment of oocytes at meiosis. I. Environ. Mutagen. 4:563-567.

Watanabe, T., T. Shimada, and A. Endo. 1979. Mutagenic effects of cadmium on mammalian oocyte chromosomes. Mutat. Res. 67:349-356.

White, L.D. 1984. Letter from L.D. White, ASARCO, Inc., to the Carcinogen Assessment Group, U.S. Environmental Protection Agency.

Whittemore, A. 1978. Quantitative theories of carcinogenesis. In: Advances in cancer research, Vol. 27. New York, NY: Academic Press, pp. 55-58.

Whittemore, A., and B. Keller. 1978. Quantitative theory of carcinogenesis. Society for Industrial and Applied Mathematics Review 20:1-30.

Wynder, E.L., K. Mabuchi, and W.F. Whitmore, Jr. 1974. Epidemiology of adenocarcinoma of the kidney. J. Natl. Cancer Inst. 53(6):1619-1634.

Wyrobek, A.J., and W.R. Bruce. 1975. Chemical induction of sperm abnormalities. Proc. Natl. Acad. Sci. (U.S.A.) 72:4425-4429.

Zasukhina, G.D., T.A. Sinelschikova, G.N. Lvova, and Z.A. Kirkova. 1977. Molecular mutagenic effects of cadmium chloride. Mutat. Res. 45:169-174.